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CALLING ATTENTION TO 470

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THE PROMISE OF A NEW ERA IN AMERICAN MEDICINE*

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I

To give a commencement address in front of your Dean, is like performing slight-of-hand tricks in front of Houdini or crooning in front of Bing Crosby. Superman as he is in so many talents which an ambitious commencement speaker should possess, he knows more medical history than a certain well known person at Johns Hopkins, more medical politics than the prince of medical politicians who must here go nameless, more medical economics than a particular member of the Social Security Board in Washington whose name incidentally, has never been a military secret and he thinks he knows more medical ethics than I do. And it is on this last point that we have crossed swords, sometimes in the presence of our dueling seconds and sometimes without them, in fair play and in less fair. And here I am invading by his own invitation, the domain in which he reigns, he rules, he presides, he governs—for further synonyms of what he does, see Roget's Thesaurus, pages 254 to 322—he has invited me down here so that he might show you how inadequate as commencement speakers are even the best of us deans when compared to your Dean.

And I have accepted his invitation, first of all, because I like Chauncey Leake even though he always gets the best of me and secondly, because I like medical students, even those in the State of Texas, and thirdly, because I have not given a commencement address to the Texas students before and I want to give it. I take the same pride in giving this commencement address as the Indian did who added another scalp to his collection. After all, I am here at a university at which I have not spoken before and I am attempting to rival some of the other deans who pride themselves on their collection of what might be called "commencement conquests." In other words, by coming here, I am feeding the vanity of my own ego, first

*Graduation address by the Dean of St. Louis University School of Medicine, at The University of Texas Medical Branch, Galveston, March, 1946.

of all, because I wanted to visit Dean Leake and secondly, because I wish to add another university commencement to my triumphs or, you will undoubtedly say, my failures, and lastly, because in achieving the latter, I shall have secured the gratification of saying what I think before people who are not prepared to answer back, because they are too polite to do so though goodness knows it might happen that the patience of even a Texan might be exhausted and in his impetuosity to relieve his feelings, he may still resort to Texas tactics.

II

Of course, I was distressed about the choice of a subject, particularly because of my anxiety not to waste the precious time of the new doctors on graduation day and of the old doctors who constitute your Faculty. I can be optimistic or pessimistic without serious disequilibration of my mental veracity, for as at all times so in this and as in all other fields, so in the field of medicine, no social or intellectual phenomenon takes place with one hundred per cent efficiency. One hundred per cent efficiency belongs into the area of perpetual motion or squaring the circle or the fourth dimension. In every human phenomenon, there are good points and bad, bright spots and dark, sweet experiences and bitter, triumphs and failures. You can emphasize the failures or the bitterness or the darkness or the malice or you can emphasize the triumphs or the sweetness or the lightness or the goodness and accordingly, your outlook will be on the silver lining or on the blackness of the cloud, on the scent of the rose or on the dankness of the soil from which it sprang, on the gorgeous cardinal flame of the evening sunset or upon the storm which has just passed and which has played havoc with the hopes and visions of man.

And so, I toyed with the idea of presenting the trends in medicine today and in medical education, perhaps to portray the threats and menaces to our cherished ideals, to analyze the destructive forces which despite the recognized triumphs of medicine are recognized also to hold in them pent up energies for human destruction. It has been said with no small measure of truth that every new discovery brings a new danger to mankind, not necessarily in the same order in

which the discovery was made but sometimes, we must pay for the gain of comfort on the physical plane with the loss of virtue on the moral, with the gain of wealth in the monetary realm, with our pauperization in the spiritual realm.

But I desire my first talk in this University and in this Medical School to sound a note of optimistic hope. I should like to tell you what form such vantage points as I enjoy by reason of contacts with many diverse kinds of persons, I think I know is happening beneath the surface of medicine and beneath the surface of the thoughts and emotions of those who use medicine. To do this, it seems to me I must tell you, first of all, what I think has been the immediate past of medicine and by the immediate past of medicine, I mean the past of the last five, six to ten years. I know that in doing this I am exposing myself to your ridicule or to your contradiction, to your irritation or to your criticism but I know also that I am exposing myself to your possible approval and your possible endorsement and your possible acquiescence and your possible sanction.

I think we have passed through a period which is none too complimentary when one views the whole history of medicine. It was a period, and I use the past advisedly because we have already penetrated two months' worth into 1946 and about eight months' worth into the postwar period, a period of analytic medicine, mechanical medicine, economic medicine, partitive medicine, precipitate medicine, turbulent, restless, irritating medicine; when things had to be half done, half assimilated, done on impulse; when one discovery crowded another and when there was no time for the careful evaluation of step by step before taking the next step; when there was no time for fitting the stupendous discoveries of the sulfon drugs and penicillin therapy and insect control and serum therapy and surgical simplification and anaesthetic diversification into the total pattern of medicine but when like the pattern of the day by day newspaper, you read of murders in one column and the canonization of saints in the next column and the dedication of a church in the same column with kidnapings and international complications and Congressional investigations of deceits and peculations. If I were

a phrase maker, I would try to find a word to describe the last ten years of medicine in terms of this comparison which I have just used. It was an era of medley medicine, of headline medicine, sensation medicine or any other term which you might care to suggest things which have to be fitted together to make a system and to produce coherence and cohesion, unity and uniformity, rather than things which have been fitted together and which have given strength and significance and power through their absorption into the sum total of human experience and their integration into the sciences and arts that deal with man. There was, in other words, in this period just past, a vast emphasis upon biochemistry as medicine or serology as medicine or physiology as medicine rather than upon medicine as it affects the destinies of man. Needless to say, such eras are essential. They are not the eras of real growth but they are the eras of the production of the elements which will be absorbed later on in the production of growth. These elements are to the real growth of medicine what the growing wheat and corn in the field are to the tissues and sinews of the healthy man.

As I see it, the period has been a period of accretion and addition rather than of assimilation. Research has flourished, research in the thousands of nooks and corners where the light of understanding has not heretofore penetrated.

Now the characteristics of such a period, assuming as I hope I may that my description is somewhat correct, are these, besides the occasional unexpectedness of discovery: unrelatedness, vagueness and occasional irresponsibility with reference to the implications of this or that discovery and so I believe that the traits of the physician in this era which I am describing have paralleled the development of the field. The physician, that is, the practitioner as well as the research workers have all been feverish in their activity. They have been the rapid readers of rapidly prepared and instantly published papers; they have been less critical of results and have been laudatory of experiments and the experimental method; they have been proclaimers of the omniscience of medicine and its omnipotence; they have been prophets of the conquest of disease by science; they have, as it were, become advertisers of the achieve-

ments of science; they have appealed to the populace, superficially rather than fundamentally; they have been students rather than scholars; they have sought information rather than knowledge; they have retailed skills to their patients rather than medical care; they have exercised ingenuity in meeting a situation rather than the insight that comes from truthful penetration. And so, the social mind which is always deeply interested in medicine has reacted to the temper of the physician. There has been an unprecedented increase in the number of foundations and a mushroom growth in the older foundations traceable, no doubt, in some instances to tax exemption but, nevertheless, inspired by the prevailing psychology. There has been a multiplication of medical shibboleths, such as, the socialization of medicine, the industrial applications of medicine, the social component of disease, the importance of medical administration, of such terms that can be given a thoroughly good meaning consonant with the highest requirements of medicine but which have been used all too frequently in the last decade to disguise an attack upon medicine proper to effect the lay control of medicine and in the course of time, the complete laization of medicine.

And the graduate of medicine in the last decade has felt some of this. Perhaps he has gone beyond his own faculty since, as I see it, the students of our schools of medicine are the recipients at the same time of the pressures of the people from below and the pressures from the faculties above and the thoughtful members of our student bodies in our schools of medicine are those who are laboring to affect the reconciliations between so-called socialized and so-called individualized medicine, terms which, to my mind by no stretch of the imagination or by no application of logical reasoning, can be made to mean what the respective words seem to imply.

III

And now, why do I speak of the coming period as effecting a change in all of this? First of all, I do not even know whether we are in a new period or whether we are approaching or whether if we are approaching it, how long it will be before we are in the midst of it. I say this because I do not know

how much longer this period of feverish activity will continue but I fondly hope that at least this is true, namely, that the cessation of the accelerated program in education may synchronize with a more leisurely assimilation in the research areas and a more responsible application of the new discoveries in medical practice.

Do I have any reasons for this hope? Yes, and the reasons are numerous as well as cogent ones. There are beginning to appear more and still more, numerous and incisive studies which caution us against the unwarranted and undue generalizations concerning new drugs and new procedures and new therapeutics. More exact quantitative determinations, more precise statistical characterizations, more critical evaluations of clinical results, more careful analyses of autopsy findings and wider discussion of results in our pathological clinical conferences, all these and many other procedures common in medicine, have made us aware that the first paeans of celebration and rejoicing must be modified by the sober truth of caution. Secondly, voices are being raised to indicate that there is a difference between omnipotence and great power and that not every victory is a conquest. Medicine has done much to reduce the incidence of disease and to lengthen the span of human life and to facilitate the better living of those whom it has rescued from a premature grave. Yet, the clammy hand of death can still snatch many an infant from its mother's breast and many a child from the guiding hand of its father. And there is misery amongst the old and the fear of sickness among the middle-aged and the dread of many a disease in the heart of a woman and a mother.

The still voices, timid as yet but to me extremely significant, are beginning to talk less of what medicine has accomplished than of what medicine must still seek and strive to accomplish. There are those who are beginning to think of the time when there will be a limit to the processes of prolonging human life and many such a thinker has pointed out the sophistry in expecting an unlimited continuation of the achievements of medicine.

And again, we are beginning to think more and more of the medical man as a man not merely of science and a man of

art but also a man of profound comprehensive culture. We are beginning to realize that strange as it may seem, there is humaneness in science, there are philosophy and poetry inherent in many a scientific fact; there are ethical values in seemingly the plainest of scientific statements. You may create or you may annihilate a human being, a human family, a human community, a nation, a brotherhood of nations by a word of misplaced advice, contraceptive advice perhaps, or advice which purports to save the embarrassment to an individual by disregarding completely the harm which such selfish good may cost to the family of a physician's patient or the community in which he carries on his activity.

Faith is not inconsistent with science and when I say this, I do not merely mean the faith which each one of us extends to the other in human relationships but I mean also the faith which each one of us who is not an agnostic or an atheist extends to the God of this universe through the acceptance of our conclusions of the reason and the still more difficult acceptance of the content of His divine revelation. Medicine must reckon with all this. The day is past when medicine was regarded as atheistic; the day is past when the philosophical tenet of medicine was materialism; the day is past when the basic approach of the physician to the patient was through a false broadmindedness which prevented one human individual in his relations with the other from saying what he really thought and believed and when there had to be deceits to cover a fanaticism and a bigotry unworthy of refined and cultured Americans whose basic tenet in life was the acceptance of the first sentence of the American Constitution.

All this is deeply related to medicine and we have among medical people today, an outspokenness and a frankness less reminiscent of the days of two decades ago than suggestive of the future program when in the words of the motto of one of our great universities "Veritas vos liberabit." We have heard only recently the President-elect of the American Medical Association make his talk on the soul of medicine. We have seen those who have labored most assiduously during the war under the auspices of the Office of Scientific Research and Development make their pleas for the guarantee of freedom if

the Federal Government undertakes the subsidization of research in the medical fields. We have heard a quieting of the clamors for the socialization of medicine and more eloquent demands for the liberation of medicine from unwarranted control. We are beginning to hear more and more insistently the insistence upon the integration of medicine through the biological entity which we call man. We are realizing the dreadful import of the diseased mind in the biological economy of man. We are emphasizing not so much the economic losses but rather the human losses entailed by the preponderance of mental and nervous diseases and we appreciate more and more the responsibilities of the physician in neglecting the mind while he treats the body. I am even inclined to say that there are tendencies among the medical men today to pay attention to the soul rather than to ignore it in the approach of the physician towards his patient. All of this means that we seem to be standing at the beginning of a new age, an age of which the whole man, body and soul, mind and emotions, the physical as well as the mental environment will really and truly be drawn within the responsibilities of medicine. All of this, inclusive of the ethical considerations without which the medical man must necessarily fail to live up to his highest possibilities.

IV

And what will all of this demand of the doctor of the future? It will demand a higher culture, a broader competence, a more fundamental responsibility; a higher culture because it will mean that the physician will be called upon to find human significance in more things, events and truths than he has ever been called upon to do in the past; a higher competence not merely because there are more areas and skills in which to be competent but because the skills of the future will be more complicated than the skills of the past, will be subject to more modifications, will be exposed to greater ineptitudes; a more fundamental responsibility because the use of the findings of science as they are assimilated into the system of medical practice will reach into the inwardness of the lives of men, into their hidden experiences, into their deepest rela-

tionships, into the totality of man's experience which range from his responsibility for his most hidden acts performed in the lonesomeness of his private chambers to his most public acts performed under the searching light of public opinion. The world expects the doctor to be superior in every way. It is scandalized if the doctor fails to achieve the level which public opinion expects of him. But there is a higher responsibility and that higher responsibility is responsibility to God Who is really omniscient and omnipotent and Who will demand of each of us, an accounting proportionate to the dignity, the sublimity and the extent of our calling and among the merely natural vocations, that of the doctor is undoubtedly, the highest.

Gentlemen, if my reading of the times is correct, you are the vanguard of a long list of men who will follow after you to march into a new chapter in the history of medicine. You will stand in higher honor than any of your predecessors; you will have greater opportunities, greater satisfactions, greater responsibilities than any of your predecessors; you will look back upon the most prolific period in the history of medicine when new ideas and new facts about life and new materials for the promotion of man were all revealed through the processes of research and the enlightenment of God to this, the greatest of the professions for human betterment. Your Medical School will just now place upon you the stamp of its approval to tell you that she trusts you to achieve all of those things which I have just suggested to you. Will you meet the challenge? Will you be able to face the future, conscious of the fact that no other graduates have had as much to take away from their Alma Mater as you have today? You are the favored children of medical history to date, the privileged offspring of the greatest of human vocations. Be worthy of your profession, of your responsibility before God, of your responsibility before the tribunals of your own patients who will praise or condemn you in proportion to your ability to reach what in their confidence in you and their love of you they have a right to expect of you.

THE ACTION OF QUITENINE ON THE LIVERS OF OPSANUS TAU AND TAUTOGA ONITIS

CHARLES H. TAFT AND J. A. PLACE*

When quinine ($C_{20}H_{24}N_2O_2$) is treated with potassium permanganate, the vinyl group is oxidized to a carboxyl group yielding quitenine ($C_{19}H_{22}O_4N_2$), von Oettingen (1933). This is probably the same as the dihydroxyquinine of Kerner (1870).

While this substance does not possess great pharmacological activity, considerable work has been done with it. Herschfelder, Jensen, and Swanson (1923) found it to be less toxic to rats than quinine and to have some antiseptic properties. Dixon and Premankur (1927) confirmed this and announced that it possessed local anesthetic properties probably due to its effect on the nerve endings. Giemsa, Weise, and Tropp (1926) state that it is ineffective against avian malaria. Dauber (1920) reported on the effect on the rabbit kidney. When the urine was kept acid by a diet of oats, there were casts, albumen, and blood in the urine, and the epithelium of the tubules was damaged. Lipkin (1919) inoculated fresh sheep and guinea pig liver with quinine for 18 hours and found that a part of the quinine had been converted to quitenine. Dawson, Vos and Little (personal communication) noted that deaths from quitenine occurred later than with other cinchona bases (5–7 days as compared with 1–2 days). Rabbits given 2 mgm./mol./kgm. subcutaneously showed oliguria or anuria for 24–48 hours. Their urine later contained red blood cells and albumen. These rabbits were sacrificed on the 15th day, and the kidney volumes compared: mean kidney volume of the quitenine rabbits 13.2 ± 1.1 cc.; mean kidney volume of the control rabbits 8.0 ± 0.5 cc.; the difference is statistically significant. The kidneys of the quitenine rabbits were a peculiar cafe-au-lait color. Kerner (1870), Halberkann (1919), and Nierenstein (1919) claim to have isolated quitenine from the urine of people taking quinine. Of the various species of vertebrates

*From the Departments of Pharmacology and Anatomy, The University of Texas Medical Branch, Galveston, and the Marine Biological Laboratory, Woods Hole, Mass. Received for publication, March 21, 1946.

injected subcutaneously with quitenine, all except the frog show large sloughs at the site of the injection. Taft (1940), Taft and Place (1944) showed that quitenine was much more damaging to the tubules of the kidneys of the Tautoga onitis than those of Opsanus tau.

Quitenine base is quite insoluble, so it was injected as the dihydrochloride. Quitenine 1.035 gms. plus 2.5 cc. 2 N. hydrochloric acid was made up to 10 cc. with distilled water, giving a ¼ molar solution or roughly a 10% weight-volume solution. When this is injected in the dose of 8 cc./kgm., one has injected 2 m.M./kg.

The fish used were kept in the portable glass tanks at the Marine Biological Laboratory and were supplied with running sea water at all times. They were not given food during the experiment. They were kept in the tanks a few days before being used.

The fish were removed from the tank, wrapped in a tared towel, weighed rapidly, and then injected subcutaneously about 2 cm. laterally to the dorsal fin and returned to the tank. The doses used for both species were 4, 8, and 16 cc./kgm. of the ¼ molar solution of quitenine dihydrochloride. The fish were out of their native element probably about a minute and a half on the average and did not show any evidence of damage from having been out of the water for this length of time.

After varying intervals of time, the fish were removed from the tank, killed with a blow on the head, and rapidly autopsied. The livers were removed and immediately placed in Bouin picro-formal solution for a week and then transferred to 70% ethyl alcohol in which they were kept. Sections were cut 6 mu thick and stained with hematoxylin and eosin or iron hematoxylin.

The fish used were of either sex and varied in weight from: for the toadfish 100 to 620 grams and for the tautog from 146 to 587 grams.

A total of 52 toadfishes were injected with different doses of quitenine. These all showed sloughs at the site of injection in a day or so. The 38 tautogs injected with different doses also showed sloughs. These sloughs varied in size from about that of a quarter to more than 2 inches in diameter. They did

not apparently bother the fishes very much. They were able to swim about normally. Due to the long lasting local anesthetic action of quitenine they were probably painless. There was no visible sign of pus or fungus infection in the sloughs. It is very probable that the water and salt metabolism was upset by this injury to the skin. It seems very doubtful whether this interfered in any way with the results of these experiments as there were sloughs of equal size in both types of fish and any error introduced by this source should be equal in each case.

In the toadfish on examining the viscera, there were no abnormal conditions in the circulatory system or intestinal tract. In a few cases with the dose of 16 cc. per kilogram the liver was very mushy. The gall bladder in the normal toadfish appeared a bluish purple. In the injected fish the color varied; bluish purple, yellow, green, pale pink, orange, and various shades of green, and brown. There was no apparent correlation between the color of the gall bladder, the size of the dose or the length of time after injection that the fish was killed.

In the tautog on gross examination, the picture was essentially the same as with the toadfish. There was no damage to the circulatory system or digestive tract. In one or two cases the liver was abnormally soft. In all cases the gall bladder was a greenish blue, as it was in the uninjected fish.

The great variation in color of the bile of the toadfish with different doses of quitenine is shown in Table 1. The variations in the color of the bile of the toadfish deserves some attention. The presence of white, pink, gray, and light green bile suggests that there is little or no bile pigment present in these cases. The pink might be due to the presence of a little blood in the white bile where there was no pigment present. Just what the action of quitenine is in interfering with the production of the bile pigment is not clear.

It is possible that this color change in the bile might be due to any one of the three following suggested mechanisms or a combination of them:

TABLE 1

Dose cc./Kgm.	Days after Injection Killed	TAUTOG No. Fish	TAUTOG Liver	TAUTOG Gall Bladder	TOADFISH No. Fish	TOADFISH Liver	TOADFISH Gall Bladder
0	....	12	4 yellow 2 red 5 reddish brown 1 brown mottled with white	1 empty 11 blue	13	9 yellow 2 brown 2 yellow mottled	9 blue 3 purple 1 empty
4	4	6	1 brown mottled with white, 1 green, 3 brown, 1 red	6 blue	6	6 brown	5 blue 1 pink
8	2	5	2 reddish brown 2 brown	5 blue			.....
8	3	4	2 brown mottled with white 1 olive green 1 brown	4 blue	....	.....	.....
8	4	6	6 brown	6 green	12	6 yellow 6 brown	1 blue gray 3 pink, 3 gray, 3 blue
8	7	5	1 red brown 2 green brown 2 yellow brown 1 soft	5 green	12	10 yellow, 2 brown, 2 soft, 1 swollen, 1 hemorrhagic	4 yellow 3 green 1 brown 1 pink, 2 purple
16	1	....	.....	....	2	1 red brown 1 yellow	1 orange 1 yellow
16	2	1	Brown	Green	4	2 yellowish pink, 1 orange, 1 light brown, 1 soft	3 orange 1 light green
16	3	2	2 brown	2 green	5	3 yellow brown 2 light brown 1 soft	3 orange 1 orange green 1 white
16	4	9	2 brown, 1 pinkish brown, 2 yellow brown, 1 yellow, 1 olive green, 2 brown mottling	3 green 6 blue	9	5 brown 4 yellow 1 soft	2 blue 1 gray green 2 orange 3 green
16	5	....	.....	.....	2	1 light brown 1 yellow brown	1 orange 1 light green

Table 1. Shows color changes in the bile of Tautog and Toadfish induced by different doses of quitenine.

(1) In some manner quitenine causes an increased oxidation of the bile pigment, the lighter the color the more complete the oxidation. Quitenine in itself can hardly be considered an oxidizing agent but it might act as a catalyst for some oxidizing system already present or interfering with some redox system by action on enzymes.

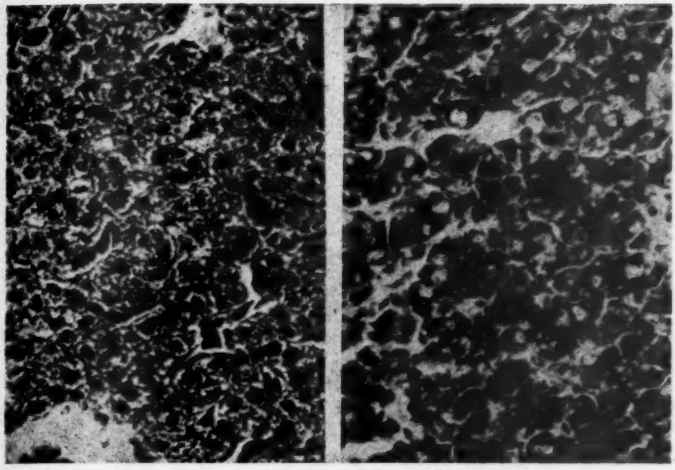
(2) There is little or no bile pigment present due to diminished production. The von Kupffer cells in the normal fish liver are very few and indistinct. In the treated fish there was no difference in the microscopic appearance of the von Kupffer cells from the normal.*

(3) There might be a direct chemical combination between the bile pigment and the quitenine. This is the most unlikely suggestion of all unless Opsanus bile differs from that of other animals. These color changes are not seen in the tautog bile nor in the bile of mammals or amphibians that have been injected with corresponding doses of quitenine.

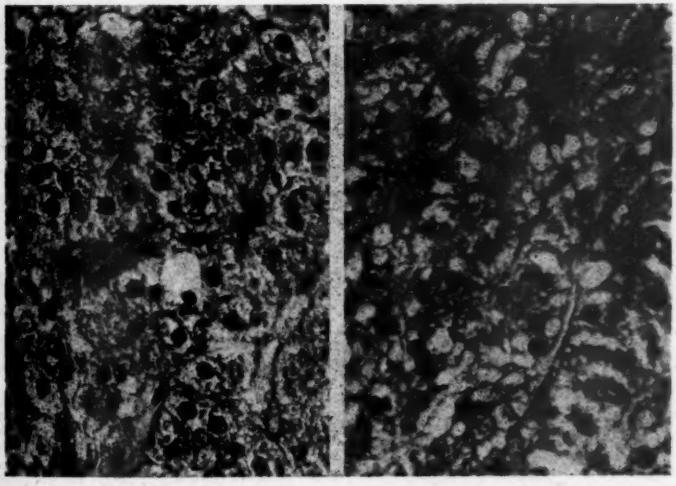
From microscopic appearance the structure of the tautog and toadfish liver is essentially the same. Each is poorly lobulated with hexagonal arrangement about a central vein. The periportal areas with their vascular and biliary channels are extremely irregular. The lobules are surrounded by many interlobular blood vessels and pierced by a network of sinusoids (hepatic capillaries). Within these sinusoids the von Kupffer cells are few and indistinct. The liver and pancreatic tissue intermingle in a manner intermediate between the hepatopancreas of invertebrates and the completely separate glands of mammals. A layer of pancreatic tissue approximately two cells thick extends like a cuff over the separate interlobular vessels and over the groups of vessels and bile ducts usually found in periportal areas. The pancreatic tissue varies from several cells in thickness to a layer so thin around small vessels that individual cells lose their identity. It is distinctly exocrine, no islets of Langerhans having been observed. The hepatic cells are arranged in anastomosing cords extending from central vein to periphery of the lobule similar to that of other forms. They are polymorphic in shape with a definite

*We are greatly indebted to Dr. N. D. Schofield of the Department of Pathology for a careful study of these slides.

PLATE I



Tautog liver uninjected. Tautog liver injected.



Toadfish liver uninjected. Toadfish liver injected.

Plate I. Tautog and Toadfish livers of injected and uninjected fish, dose in both cases 16cc./Kgm. for 4 days. X 425.

cell membrane, comparatively clear cytoplasm, more or less chromatic nucleus with a densely chromatic nucleolus. This appearance is extremely variable depending upon their particular functional state. Plate I.

The individual differences between the liver of tautog and toadfish are negligible. There is definitely a greater percentage of pancreatic tissue in the liver of the tautog than in that of the toadfish. The cell membrane of the hepatic cells is more distinct in the toadfish and the cells are larger, cross-section measurements showing an average of 16 microns for toadfish and 12 microns for tautog.

The injection of quitenine has a definite damaging effect upon the liver of both tautog and toadfish. The damage is due to the drug itself since the injection of acid alone has been shown to have no effect upon the liver parenchyma. The amount of damage is in direct proportion to the dosage and is much less than that upon the kidney (Taft and Place, 1944). The extent of damage is greater in the tautog than in the toadfish liver as was the case with the kidney of the same animals. The pancreatic cells of the hepatopancreas were unaffected.

TABLE 2

Toadfish	*Tautog*
4 cc./Kgm. 4 days	
Least damage. Nearly normal.	Slight cloudy swelling. Least damage.
8 cc./Kgm. 4 days	
Little damage. Mostly normal.	Slight cloudy swelling, of albuminous and parenchymatous degeneration type.
8 cc./Kgm. 7 days	
Some very slight parenchymatous degeneration. For the most part nearly normal.	Fatty metamorphosis. Albuminous degeneration. Hydropic degeneration.
16 cc./Kgm. 4 days	
Damage moderate. Some fatty metamorphosis. Some parenchymatous degeneration.	Marked diffuse fatty metamorphosis. Little diffuse parenchymatous degeneration. Damage widespread.

Table 2. Comparative damage to livers of Toadfish and Tautog caused by injection of different doses of quitenine.

Microscopic study of the livers of the fish showed in some cases considerable damage, the extent varying with the dose. This information is shown in tabular form in Table 2 and illustrated by the photomicrographs in Plate I.

We have not been able to find any references to liver damage caused by quinine and it seems extremely interesting that a detoxified form, *i.e.*, vinyl group oxidized to carboxyl, would cause such liver damage. If as has been claimed quitenine is metabolized in the liver from quinine this may account occasionally for some of the non-typical toxic effects following administration of quinine.

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POLEOMYELITIS, CLINICAL ASPECTS AND EARLY DIAGNOSIS*

JOHN A. ANDERSON

The State of Utah has had the unfortunate experience of having 662 cases of poliomyelitis in the period of 1943 to 1945, exclusive. It was thought advisable that a description of the nature of these epidemics and the experiences encountered in the care of these patients would serve to emphasize some points considered to be important in the early diagnosis of poliomyelitis. The epidemic of 1943 was decidedly different from the epidemic of 1945, both as regards the type of clinical disease and the mechanism of its distribution throughout the state. In 1943 the first cases encountered as early as January and February were of a sporadic nature, occurring in various parts of the state, remote from each other. However, about the first of June, cases made their appearance in an area near Provo, Utah, some 36 miles south of the center of population which is in Salt Lake City. The distribution then spread somewhat in a radial manner until it reached Salt Lake City in August and September. There were 43 cases from the entire state in August and 211 cases during the month of September, better than 50 per cent of which came from the Salt Lake City area. A survey by interview and visit to the homes of 241 cases revealed the following information. Fifteen per cent of the cases studied were found to have a definite history of direct contact with a paralytic case of poliomyelitis. Watermilk supply were investigated in practically every area of the state but failed to reveal any information in regard to the source of the virus. Only 4.1 per cent of the children investigated had been swimming in pools, creeks, or irrigation ditches within the two-week period previous to their illness. Forty-three and five-tenths per cent (43.5%) of the children, however, gave a history of having been bitten by mosquitoes or flies within this period. It was found, however, that 206 of

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these children gave a definite history of having eaten unwashed or unpeeled fresh fruits and vegetables two weeks or more prior to developing the disease. As regards the nature of the type of poliomyelitis, it can be safely said that the epidemic was of a relatively mild nature. Better than 60 per cent of the cases had little or no residual involvement. Of the remaining 40 per cent, about one-half have been left with some permanent weakness or disability of a serious nature. The other half of the remainder are only mildly incapacitated. Further indication of the relative mildness of the epidemic is suggested by the fact that only two of the 400 cases that occurred, excepting those that died, are still unable to walk about. The mortality of this epidemic was 6 per cent.

A point of interest in the 1943 epidemic centers itself around the incidence of poliomyelitis in recently tonsillectomized children. A survey conducted during the months of July, August, and September revealed that 1,499 tonsillectomies were done on children between the ages of 13 and 16 years. In this group there were 17 cases of bulbar or bulbo-spinal type of poliomyelitis, which first became manifest on an average of 15.9 days following the tonsillectomies. On an incidence basis, the figures revealed that in the general population of this same age, that 15.2 children per 10,000 child population became ill with clinically diagnosable poliomyelitis, while 40.4 children of the tonsillectomized group of the 10,000 population became ill with the clinical poliomyelitis. One hundred per cent (100%) of the cases of the recently tonsillectomized were of the bulbar or bulbo-spinal type.

The epidemic of 1945, in which 262 cases occurred, was different in many respects than that of 1943. Two hundred thirty-two (232) of these cases were admitted to the Salt Lake General Hospital, providing an excellent opportunity for thorough evaluation. In this year no increased frequency of cases in the state was evident previous to the month of June. The first cases appeared in an area about two miles south of Salt Lake City, spreading radially into Salt Lake City and its environs. Sporadic cases in remote areas of the state occurred during the peak of the epidemic. The history of contact to a clinical case of poliomyelitis was much more frequent in this

year. Another point of difference as compared with the 1943 epidemic is in the per cent of bulbar cases that occurred. In 1943, 9 per cent of the 400 cases were of the bulbar or bulbo-spinal type, whereas of the first 126 cases which occurred in 1945, 46 per cent were of the bulbar or bulbo-spinal type. The mortality among this group was 16 per cent. However, the total mortality for the entire 462 cases in 1946 was 8 per cent. Because of the emphasis on the importance of tonsillectomies in 1943, most of the physicians within the state discontinued tonsillectomies during the summer months. In spite of the fact that 46 per cent of the initial 126 cases were of the bulbar or bulbo-spinal type, only two of these were preceded by a recent tonsillectomy.

One other point of comparison worthy of mention is that a history of prodrodmal manifestations was much more frequent in the 1943 epidemic. The outset of the cases in 1945 tended to be more exclusive with the pre-existent prodromita.

Early Signs and Symptoms

In discussing the early signs and symptoms of poliomyelitis, it must be stated frankly that it is impossible to make a diagnosis of poliomyelitis from only the prodromal signs and symptoms. These are common to any mild respiratory or gastro intestinal infection. During an epidemic, however, one is confronted with a great many cases in which vomiting, diarrhea, fever, headache, and general malaise are present which are of course watched with suspicion as to the possibility of a subsequent development of clinical diagnosable poliomyelitis. It is necessary, however, to emphasize several points. Abdominal pain in the prodroma of poliomyelitis may be of a severe nature, simulating acute appendicitis. The differentiation is extremely difficult. Inability to rule out an attack of acute appendicitis in two of our children necessitated an operation. Both of these children were found to have a normal appendix, but two and three days subsequently, developed the characteristic signs of poliomyelitis. One further observation of interest which has not been given much emphasis is the presence of small flecks of blood in the stool in some of these children. This was observed on four occasions in 1945 in

children who subsequently developed clinical poliomyelitis. It is necessary to state that the laboratory examination is of little or no assistance. The sedimentation rate was nearly always normal. Leukocytosis with a polyneutrophilia was present at times. One must conclude with the statement that there is, as far as is known, no way in which a definite diagnosis of poliomyelitis may be made in the prodromal stage.

Abortive Poliomyelitis

It has been stated that during epidemics that the frequency of abortive poliomyelitis is six times as great as paralytic poliomyelitis. Here, it is known that the virus is present in the nasopharyngeal secretions and the gastrointestinal secretions of these cases. It must be assumed that the virus is also present in the central nervous system.

Clinical evidence of neurologic dysfunction is present in these children. If one excepts the presence of anterior horn damage in these children because there is no paralysis or evidence of lower motor neurone involvement, one can possibly accept the fact that some neurological disorder is present. Recent investigations have emphasized the fact that the anterior horn cell is not the only cell which can be involved in poliomyelitis. It is sufficient evidence to indicate that the entire cord and central nervous system may be involved in a non-specific way with edema and inflammatory process. More specific localization, however, has been shown to be present in the posterior horns and in the root ganglia. Kabat has emphasized the importance of internuncial cell damage, and more recently Bodian has emphasized the presence of involvement of the reticular substance of the brain and upper part of the spinal cord. These latter two, from the present knowledge as to their function, offer some explanation for the loss of inhibitory function that is present in early poliomyelitis.

In the light of these more recent observations of a pathologic nature, one is able to offer some explanation on a neurophysiologic basis for the signs and symptoms in abortive poliomyelitis. Stiff neck and back is a sign that is present in nearly every case of abortive or early poliomyelitis. The exceptions appear to occur most frequently in the very small children

under the age of two. In 1943, 33 children were observed in which it was felt that the diagnosis of abortive poliomyelitis was justified on the basis of stiff neck and back and increased cell count in the spinal fluid, the presence of prodromata, and the subsequent clinical course. These children were found to have fever, headache, stiff neck, stiff back, and bilateral reduction to straight leg raising. It should be pointed out that the reduction in straight leg raising is not always the same for both legs. Many children showed resistance and pain when one leg was elevated to an angle of 30 to 35 degrees, whereas the other lower extremity could at times be elevated through the complete range of motion with only slight discomfort occurring at the maximal point. This asymmetry in the lower threshold for the stretch reflex suggested the possibility of involvement of cord substance because of the suggestion of a reciprocal innervation imbalance.

The pain in abortive poliomyelitis is a highly variable factor. It varies from a very mild sense of discomfort on motion of the extremity to a highly painful degree so that the child does not permit any disturbance or movement whatever. As suggested above, the presence of involvement of the posterior horns and the root ganglion cells offers an explanation for the pain in poliomyelitis. It is manifest most often by voluntary resistance on movement of the extremity, back, or neck through its functional range of motion. Pain in the muscle itself is also present. Pressure of the muscle belly, particularly of the insertion of the tendon with the muscle in the involved extremities, gives evidence of a reduced threshold to pain perception. Occasionally the pain factor in poliomyelitis is so severe that one sees the child that refuses to move any of his extremities, giving the appearance of a complete paralysis. However, a few weeks later with the subsidence of the pain, the child gives evidence of complete functional return, without significant residual weakness or paralysis.

Hyperreflexia is commonly present. It may be present in the uninvolved extremity and is also present in the involved extremity. It suggests the possibility of a loss of an inhibitory mechanism in the reflex arc.

There are further several minor points that deserve some consideration. Fasiculation is not uncommonly present in early poliomyelitis. The subjective signs are of interest. The mother states that because the child was ill she permitted him to sleep with her and noticed that he was "jumpy" in his sleep. The older child sometimes brings out the fact that he was unable to sleep because his legs felt funny. Sometimes they "jerked," or they felt as if they were "jerking." Fasiculation can best be described as a "tic"-like mechanism due to a spontaneous uncontrolled contraction of a fasicular muscle bundle. Some children stated that one finger jumped uncontrollably on occasion. Contractile spasm of the hand at the wrist or the arm at the elbow and at times the foot, was present. This consisted of a unilateral uncontrollable flexion of the hand, such as is seen in infantile tetany. Several of the parents stated that it was associated with pain and that they had rubbed the extremity in an attempt to release the contraction. Visual disturbances were present infrequently. Patients complained of an inability to focus the eyes while reading because of a "jumpiness." It always demonstrated a rather coarse astigmia, not at the lateral or medial position of the eyeballs but somewhat central in nature as the finger was moved in an arc in front of the patient's eyes in an examination for extraocular eye movements. It was suggested that this disorder may again be a loss of inhibitory control necessary in the coördinate activity of the extraocular muscles and the accommodation response. This is occasionally seen in cases of encephalitis, suggesting involvement of the third nucleus and its associated tracts. The usual methods for the determination of a disorder in the vibratory sense do not reveal any significant disorder in poliomyelitis. However, it has been shown recently with the use of the pallesthesiometer that it is a disorder in this function.

Laboratory findings in abortive poliomyelitis are of very little value, with the exception of the spinal fluid. The sedimentation rate was nearly always normal and when elevated, other reasons for its elevation were usually found. The white count and differential are of little help. Spinal fluid findings, when present, were of great value. It has been stated that the

cell count of the spinal fluid in abortive poliomyelitis is not as high as that found in the paralytic case. This is not always true. The cell counts varied in abortive cases from zero to 550 cells with at times a predominance of polymorphonuclear cells, and at times a predominance of lymphocytic cells. Fifty to as high as 135 mgm. per cent of protein is present in the spinal fluid. The majority of the cases, however, show only a slight increase.

Paralytic Poliomyelitis

It is not necessary to dwell at great length on the clinical diagnosis of paralytic poliomyelitis. The presence of weakness, diminished reflexes of a localized, generalized, or spotty nature, associated with the above signs and symptoms described under abortive poliomyelitis, are nearly always sufficient to make a clinical diagnosis. It must be stated, however, that at times, when complete paralysis of one extremity is present, the occurrence of spasm or limitation of motion of the extremity is not always present. This is particularly true for very small children who present themselves early in the course of the disease with a completely paralyzed extremity which can be moved through the full range of motion without pain. On the other hand, one sees many cases in which a markedly weak extremity is present that is extremely tender when moved or when the muscles are pressed.

It is not known clearly whether or not the early diagnosis of poliomyelitis and the institution of proper rest is conducive to abeyance of the progress of the disease in the central nervous system. On an empiric basis however, it seems reasonable that the diagnosis of poliomyelitis should be made as early as possible. An opportunity is then provided for the provision of complete rest and the maintenance of a good nutritional state during the acute phase of the disease. One likes to believe that the institution of proper procedures early in the course of poliomyelitis reduces the incidence of the more serious forms of the disease. This, however, is without scientific support. The early diagnosis of the bulbar and bulbo-spinal type of poliomyelitis is of great importance. These children have the

highest mortality, and much can be done to avoid complications incident to deglutition and mucous aspiration. It is likewise important that early diagnosis be made because of the possibility of involvement of the respiratory muscles. One is prepared to meet many of the situations associated with bulbar or respiratory involvement if diagnosis is made early and the child is admitted to the hospital for observation.

ORTHOPEDIC TREATMENT OF POLIOMYELITIS*

G. W. N. Eggers

The first duty of the attending physician in acute anterior poliomyelitis is to make the diagnosis. When this has been accomplished, it is necessary for the physician to realize that more than medical therapy is needed. The motor paralysis of poliomyelitis causes more crippling deformities than all other acute diseases combined. The orthopedic surgeon who sees these unfortunate results of the disease and who is familiar with these can be of great assistance to the pediatrician or general practitioner in preventing deformities and assisting in the return to function the remaining functional musculature.

The disease may be divided into three clinical stages: 1. Acute. 2. Convalescent. 3. Chronic.

1. The acute stage probably covers about eight weeks of muscular tenderness to disappear, often much longer in the severe cases.

2. The convalescent stage is the recovery period with muscular re-education; substitution and re-coördination are the principal features of care during this period.

3. Chronic stage represents the period when the paralysis is residual and when deformities occur which are more or less permanent.

The Acute Stage

During the acute stage of the disease, the bed should have a plywood board under the mattress, and the patient's arms and legs should be placed in position to assume better function; that is, the feet should be supported, the knees kept straight and the hips extended. Bed clothing should be kept from the foot of the bed because the weight may cause the patient to have footdrop. The foot board is useful at this stage. The arms should not be permitted to assume internal rotation and adduction deformities. The back muscles are protected by the

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even bed or a frame may be used. The muscles should be placed in functional rest. This period is also characterized by deep tenderness. Rubbing and massage are not recommended at this time, nor should the muscles be stretched or manipulated. All of this gives rise to undesirable muscle spasm. The pain can be elicited by gently pressing the affected muscles and moving the part gently against the action of the painful muscles.

The treatment during this period is the use of heat, as packs or water immersion. The temperature should not be over 100° F. This relaxes the muscle spasm and when the treatment is combined with proper support, the tendency toward deformities is kept at a minimum. The duration of this treatment should be continued until all tenderness has disappeared before attempting functional restoration.

I might mention the use of the respirator at this time. The purpose is to assist the patient and not to assume all respiratory difficulty. Most patients have a bulbar loss involving the diaphragm or an intercostal loss involving the thoracic cord. Seldom do both occur. In the majority of cases of partial involvement, the respirator is a great aid but should not be used continuously. The patient must be made to assume his respiratory responsibility as much as he can and not depend upon artificial respiration.

The Convalescent Stage

This is characterized by functional return and muscular activity with the purpose of preventing deformity and a return to normal activity. At this time, a muscle chart should be made—an accurate evaluation of all the muscles.

Unfortunately, the system used varies with different institutions and different individuals. However, if the key symbol on the muscle chart is known, the interpretation by a good physical therapist or orthopedic surgeon is fairly accurately obtained. A convenient method is to use "poor," "fair," or "good" (normal) or clinical purposes. Numerical evaluation is quite all right but difficult regarding exact interpretation.

The patient should be given muscular training by a competent physical therapist supervised by the orthopedic surgeon.

The progress should be noted on the muscle chart and closely followed. The exercises usually start with group movement of muscles and follow with individual muscular movements. When any signs of fatigue develop, rest is given and the exercises repeated. The treatment should be performed daily and is often prolonged. There are several ways this may be accomplished: 1. A hospital clinic. 2. State care. 3. Teach the parents, especially the mother, the exercises.

Under-water exercises are very valuable and should be used when available, as a pool, Hubbard tank, or similar device.

There is a recent enthusiasm in which bracing methods are not encouraged. This is a fallacy because proper bracing is a great help and often a means to an end which permits the discarding of braces later.

I still think the therapeutic pool can be of assistance at this stage, especially in the restoration of the walking function. It also has a very desirable psychological effect because it encourages the patient since he can perform muscular functions in water that he is unable to do out of the pool.

The muscular re-education of these patients is important. It is remarkable to note the amount of function and substitution of muscles for similar function which can be accomplished by experienced physical therapists and practitioners of physical medicine.

This convalescent period should be maintained for a year or longer. The deltoid which is partly paralyzed may function again even after a longer period of time. Braces which are worn must be carefully watched, adjusted, and replaced. As soon as practicable, the bracing is removed.

The amount of recovery during this period is dependent upon the involvement of the motor cells of the spinal cord. In time, the patient will progress into the chronic stage.

The Chronic Stage

The chronic stage is the condition of permanent damage. The patient may or may not have deformities depending on the care and treatment during the convalescent stage. In some cases the damage is extensive and the result is determined

by the permanent damage. Generally speaking, about fifty per cent recover completely, twenty-five per cent have minor disabilities, twenty per cent have more extensive involvement, and five per cent do not survive. When the patient has passed all evidence of improvement, he then becomes permanently involved and may require permanent bracing, surgery, or both.

In addition to the physical improvement of these cases, one must also remember that emotional training, education, and general personality difficulties demand attention and are important in the ultimate restoration of the individual to his position in life.

Braces should be light, strong, and made of a rust resisting material. The joints should be properly placed, padded, fitted, and have joint locks of the type indicated in each individual case. The brace must be supervised by one interested in the case and not left to the judgment of a brace maker. An uncomfortable, heavy, unsightly brace discourages the wearer.

The inactive poliomyelitis case must also be watched for increases in weight. Too many of these cases are permitted to eat too much and then adiposity interferes with the walking function when it is impaired. Braces are difficult to fit and sustain on fat individuals.

When the child has a fixed paralysis, there is the final question of surgical help. The first important factor is the age of the patient. Young patients are not suitable surgical subjects; and, if any osseous surgery is indicated, they should be about nine years of age, perhaps twelve years is better because the bones are more fully developed and have less cartilage in the joint areas. Prior to this time, bracing care is the only logical treatment to those needing additional help.

The operative treatment may be said to include tendon transplantation. This assumes a variety of possibilities and requires a great deal of care and thought. A muscle may be a good flexor, but when transposed to an extensor, may or may not function. The patient has to ignore the previous function of the muscle and destroy the previous synergism present, and mentally reverse the function that the muscle previously

performed. Some individuals accomplish the change in function well, some poorly, and a few never can use the transplanted muscles.

It must also be remembered that changing the mechanical arrangement of a muscle by tendon transplantation is often disappointing. It simply does not assume the function expected and disappointment follows. The surgical procedure is not always followed by the physiologic success which seems reasonable to follow. There is always some uncertainty in tendon transplantation of muscles. I may add that entire muscular transplants are not practicable due to length and position of the nerves supplying the muscles.

The osseous surgery is of great help and very efficient in many cases. In working on the feet, one must remember the growth deficiencies and the effect of the surgical procedure on growth. The shoes are also of importancec as to position of the foot and mismating of shoes, from an economic and cosmetic necessity. The many conditions can hardly be considered at this time, but the dangle foot, footdrop, calcaneous, oquinus, valgus, varus, and various combinations of deformities are mentioned.

The hip may be in flexion, internal rotation, external rotation, or the gluteals may be involved in various ways.

One leg may be shorter than the other, and the problem of lengthening the short leg, shortening the long leg, or creating an epiphyseal arrest by fusion or deep X-ray therapy in the selected leg have their value when used judiciously. Certainly no surgery should be done on leg variations unless about three inches difference is present and the short leg can reasonably assume the duties it will have to perform.

The spine can present most discouraging disabilities. Scoliosis, kyphosis, lordosis, and the abdominal paralysis all contribute their deformities. The treatment of this condition requires study, patience, proper supporting, surgical help, and unlimited coöperation by all concerned.

The shoulder may require muscle transplantation or fusion of the humerus to the scapula. There are many possibilities of muscular improvement.

The surgical procedures are extended to the elbow, wrist, forearm, and their success depends on an accurate evaluation of the muscles available, their strength, and the patient's coöperation.

In the application of surgery, only too often we have a compromise accomplishment. Seldom do we get a perfect result but improvement is usually always obtained. One must remember the surgical procedures are limited by the available material, and surgery is usually required by the severe permanently deformed cases. The purpose of the surgery is for practical purposes and must so be accepted.

The most stimulating feature of the orthopedic efforts with the paralytic of poliomyelitis is the optimistic attitude of recovery which all seem to have and their appreciation of any improvement one may give them—small as it may seem.

PROSTIGMINE AND POLIOMYELITIS*

JOHN A. ANDERSON

In recent years clinical emphasis has been placed on the presence of an abnormally increased tonus of skeletal muscles in poliomyelitis. Clinical observations have shown, however, that there is no constant relationship between this increased tonus and the degree of motor denervation. It has been suggested that this hypertonus not only causes limitation of joint motion but its persistence over many months may lead to permanent gross deformities. Unfortunately conclusive electromyographic evidence of the existence of an increased state of tone in the resting unstretched muscle has not as yet been offered. Watkins and Brazier demonstrated spontaneous low voltage discharges arising from weakened and painful muscles while at rest early in the course of the disease, and similar spontaneous discharges of a higher voltage arising later in the disease. These latter discharges were present more frequently in muscles showing the most loss of power as compared with their antagonist which clinically showed evidence of hypertonus. The presence of these discharges suggested to them motor unit activity which were probably related to neurone regeneration in which neurone potentials were not properly inhibited.

In addition to the existence of hypertonus in the resting unstretched muscle Kabat has suggested that there is another disorder which he prefers to call a hyper-irritable stretch reflex. In this disorder there is limitation of the range of passive motion which is variable in degree from one extremity to the other. Ordinarily the limb may be moved through its complete range of motion until it reaches the inhibiting factors inherent in the anatomy of the respective joint. There is no resistance normally to this full range of motion by the muscle itself until the maximum range of the movement peculiar to the extremity is reached. In poliomyelitis, however, there

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appears to be in practically every case varied degrees of hyperirritability of the stretch reflexes, either confined locally to one extremity or generally throughout the entire muscle system. In this condition a "trigger mechanism" is set off at a lower level which initiated an opposing protective contraction in the antagonistic muscle group. This "trigger mechanism" clinically, is associated with pain in the stretched muscle. The degree of pain varies considerably from one of a severe nature which elicits violent objection on part of the patient to further passive motion, to one of only a sense of discomfort.

While the existence of these two factors of hypertonus and the hyperirritable stretch reflex in acute and chronic poliomyelitis is not denied by most observers the point of departure lies in the damage that these physiologic abnormalities may add to the already existing true paralysis on the basis of motor neurone destruction. To the minds of some it is the most damaging factor in the average case of poliomyelitis, because it permits the development of deformities in extremities that may have some residual muscle strength left. To others it is considered of little or no importance as a contributing factor to the occurrence of deformity for it is felt that the degeneration of the motor neurone is primarily responsible by a succession of histologic changes over a period of time to the development of permanent contracture and deformity.

The justification of the use of a chemical or mechanical agent in the treatment of poliomyelitis depends then on classification of the etiologic factors which lead to the permanent muscle defects which follow the disease. If hypertonus and hyper-irritable stretch reflexes are of no concern—therapeutic procedures designed to correct them would certainly be of no value. Treatment should then be directed primarily to the prevention of contracture of muscle which is degenerating because of loss of its motor neurone.

Recently considerable evidence has been accumulating to support the fact that the greatest restoration of function of the muscles in poliomyelitis is possible by the early introduction of passive and active physiotherapy over as wide a range of motion as is possible without inducing pain or fatigue in affected muscles. This program appears to be sound and for

the most part physiologic. Muscle bundles supplied by unaffected neurones should be of as much activity as is possible under the circumstances. Muscle bundles supplied by degenerated or degenerating motor neurones will continue to atrophy until some factor is found which will permit their regeneration. The value of a continuous program of full range of passive motion in partial or completely denervated muscles cannot be denied.

It is not the purpose of the paper to support either concept but to provide further evidence of the occasional value of prostigmine in modifying the hyper-irritable stretch reflex in poliomyelitis.

The effects of prostigmine on muscle function have been reviewed by Kabat. Its general pharmocologic action is now generally believed to depress the function of cholinesterase, the inactivator of acetylcholine. This permits acetylcholine in the myoneural junction to continue its action uninhibited. The ability of prostigmine to relieve fatigue of muscles in myasthenia gravis, to aggravate the muscular rigidity of post encephalitis Parkinson's disease, and to increase the fibrillation of denervated muscle is said to be due to its action on the myoneural junction. In contrast to these actions Kabat demonstrated that prostigmine lowered the threshold for the occurrence of the stretch reflex and suggested that this effect is produced by its action on the spinal cord. The investigations of Kremer and Menlis and Loveson support this concept. Kabat suggests that its action in poliomyelitis is more likely to be on the internuncial cell rather than on the anterior horn cell.

Method of Study

From July to January, 1943, 136 cases of poliomyelitis were admitted in the acute stage to the Salt Lake County General Hospital. During their stay in the hospital one-third of this group received prostigmine either orally or subcutaneously or both for one or more periods of time, varying from a few days to several weeks. Twenty-two patients were closely observed by making frequent measurements of the degree of limitations of the range of motion of all extremities and muscle groups of the body in which there was some degree of limitation.

Prostigmine was given initially hypodermically and followed by oral prostigmine for varying lengths of time from several days to as long as one month. These doses administered were usually as follows: Up to 5 years of age: 0.5 Mgm. t.i.d. subcutaneously or 15.0 Mgm. t.i.d. and q.i.d. orally; 5–10 years of age: 1.0 Mgm. t.i.d. subcutaneously or 30.0 Mgm. t.i.d. or q.i.d. orally; 10–15 years of age: 1.5 to 2.5 Mgm. t.i.d. subcutaneously or 45.0 Mgm. t.i.d. and q.i.d. orally. Atropine sulphate was not given unless the doses were increased up to the point of intolerance as manifest by abdominal cramps and excessive sweating or salivation.

The response in twenty-three cases is shown in Table I. The responses in the following children were for the most part rapid and dramatic.

Case 1: R. W. presented severe respiratory paralysis on admission to hospital and was placed in the Drinker respirator for five days. Following removal from the respirator there was a marked reduction in the stretch reflex of both legs on straight leg raising and of the right arm. A single dose of one milligram of prostigmine subcutaneously permitted full extension of the arm within six hours. On the next day the limitation of motion returned to near the original point. Oral prostigmine was then started and within two days complete extension of the arm was possible, both actively and passively without pain. Both legs also improved rapidly under oral therapy given over the next ten days. No hot packs were used.

L. P. Suffered a mild poliomyelitis on 7/25/43. An admission to the hospital on 7/28/43 intensive hot-pack therapy was given for a period of 14 days. During this time no change in the stretch reflex of the legs was noted. Prostigmine (32 Mgm.) (t.i.d. orally) was begun and within four days, both legs improved markedly. While on prostigmine the improvement in right leg began to regress. The dose of prostigmine was then increased to 45 Mgm. t.i.d. Again, the right leg responded by a reduction in the degree of limitation of motion.

D. R. A severe polio was marked paralysis of both legs. The patient was given hot packs for twenty days beginning on the twenty-second day of illness without noticeable improvement. Later, on the thirty-second day of illness, subcutaneously

prostigmine (1.0 Mgm. t.i.d.) produced a sudden and striking improvement in the ability to raise both legs, and a complete return in the full range of motion of the lower leg and on flexion at the knee. However this child had been having a gradual improvement of knee flexion in the preceding twenty days, while under the pack treatment alone. Even though the change in degree of flexion at the knee was rapid and striking, the limitation of both legs on straight leg raising was affected only for the first three days and then the rate of improvement continued at about the same rate as was observed previous to the prostigmine period.

S. D. Age seven, entered the hospital 8/2/43 with severe involvement of both lower extremities. Prostigmine (15 Mgm. t.i.d. orally) was given on the thirtieth day of illness, and continued for seven days without significant response. Prostigmine (0.5 Mgm. S.C. t.i.d.) was again started on the forty-eighth day of illness with a striking improvement in the degree of limitation of motion of the left leg, and no change in the right. However, the right continued to improve slowly and approached the level of motion attained by the left leg.

J. E. Age five. Was given prostigmine methyl sulfate (0.5 Mgm. s.c. t.i.d.) on the thirty-first day of illness without change in the already improving range of motion of the legs.

R. W. Age twelve. A respiratory case, was given prostigmine (30 Mgm. t.i.d. orally) on the fortieth day of illness with a striking improvement the first three days. Thereafter the range of motion remained the same for the next four days and then continued to improve to the point of complete restoration of the ability to raise the leg straight.

A most striking change occurred in the ability to extend the right arm—after removal from the respirator the right arm could not be extended beyond 130°. A single dose of prostigmine (1.0 Mgm.) permitted complete painless extension of the right arm to 180°. Twenty-four hours later the arm could be extended to only 150°. Oral prostigmine (30.0 Mgm. q.i.d.) produced again an ability to completely extend the arm. This improvement persisted after discontinuing the drug.

L. P. Age nine. Was given prostigmine orally (30 Mgm. t.i.d.) on the nineteenth day of illness with rapid improvement in both legs.

Under therapy, the right leg began to become worse; however, an increase in the dose of 45 Mgm. t.i.d. resulted in marked improvement.

The degree of paralysis of these children varied greatly, yet the response to prostigmine could not be predicted by the presence or absence of paralysis. At times a limb with severe involvement responded well, (D. R.) at other times a limb with little or no weakness, yet having a high degree of limitation motion, responded poorly (C. J.).

The results of the administration of prostigmine on the degree of change in straight leg raising only in 23 children are presented in Table I. The duration of treatment varied from five to thirty days or an average of seventeen days. During this period the average improvement in straight leg raising was 14° for the right leg and 16° for the left leg.

Discussion

In spite of the fact that occasional striking changes occurred in the degree of limitation of motion in these patients, it occurred for the most part within the first three days of therapy. Thereafter, even increases in the dose of the drug did not result in further sudden improvement. The average change in these patients cannot be considered significantly greater than is usually observed under heat therapy and intelligent physiotherapy. There appears to be several sequences of events in regard to hypertonus and limitation of motion due to lowered threshold for the stretch reflex. In some patients the limitation becomes more striking during the first three weeks of the disease and then rapidly or slowly improves over the next four weeks. Other patients continue with limitation of motion at the same stage for several weeks without change and then as the pain associated with motion subsides the degree of limitation improves.

TABLE I

Effect of Prostigmine on the Stretch Reflex in Poliomyelitis

Case		Age	Duration of Treatment	Change in Degrees Straight Leg Raising	
No.	Name	Years	Days	Right Leg	Left Leg
1	C. V.	14	12	0	10
2	B. H.	11	12	12	10
3	R. P.	5	14	25	35
4	J. O.	12	11	12	0
5	J. P.	3	23	15	15
6	J. E.	5	19	30	55
7	S. D.	8	5	0	0
8	S. D.	8	20	11	15
9	C. J.	12	34	27	20
10	L. S.	9	17	0	0
11	H. W.	10	18	10	15
12	C. V.	8	9	15	20
13	C. P.	6	26	5	20
14	R. T.	11	19	30	20
15	D. R.	10	21	25	10
16	T. J.	5	12	5	5
17	T. J.	5	20	22	30
18	W. H.	11	29	5	10
19	D. B.	12	18	25	10
20	B. M.	15	18	8	10
21	J. S.	12	16	16	29
22	C. C.	10	16	12	7
23	C. A.	12	....	13	20
	Average		16.9	14°	16°

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THE PHYSIOLOGICAL BASIS OF ASTHMA*

W. A. Selle

There are gaps—large, numerous gaps—in our knowledge of the pathologic physiology of asthma. True, we know much about anaphylaxis in animals; we know that human asthma is similar in some respects to the foreign protein asthma of guinea pigs. We still do not know, however, whether the dyspnea of human asthma is due primarily to bronchospasm, to increased mucous secretion, or to edema of the mucous membrane of the bronchi. We are still uncertain whether the obstruction resulting from one of these three factors is due to the antigen-antibody reaction itself or whether some chemical substance such as histamine, thought by many to be liberated during most allergic responses, is the chief cause.

A. Cause of Dyspnea

The controversy over the mechanism of dyspnea has not abated in recent years. Each of the suggested causes has its adherents. Experimental evidence indicates that bronchial constriction plays a role in the obstruction. In "guinea pig asthma" spasm of the terminal bronchiole is stated to be responsible for asphyxiation. Boughton also claims that following fatal anaphylaxis in children and adults thickening of the bronchial muscles is found. Sheppe, likewise, supports the bronchospastic type of reaction in true fatal anaphylaxis in man. Huber and Koessler contend that chronic asthmatics frequently show a thickened bronchial musculature. Against this indirect and not too convincing evidence we find the following recent statement: "Although the pathological basis of asthma was once supposed to be spasm it is a curious fact that spasm has never been demonstrated in any cases studied by bronchoscopy."† It is not curious, however, that the bronchoscope fails to reveal

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†Ohio State M.J., 41:230, 1945.

constriction of the terminal bronchi for the latter are only a fraction of a millimeter in diameter and are inaccessible to direct observation.

When bronchospasm was demonstrated to be the mechanism for dyspnea in guinea pig anaphylaxis, proponents of the constriction theory of asthma felt that they had at last found experimental proof for their contentions. Walzer, however, points out that while the anaphylactic reactions occur in the smooth muscles in animals, this tissue has never been experimentally demonstrated to be the shock organ in human asthma or in other atopic diseases of man. Walzer further contends that atopic reagins, the only antibodies demonstrated in asthma, have no affinity for smooth muscle but become as readily fixed to the mucous membrane as to the skin. This he considered as evidence in favor of the view that the mucous membranes are the seat of the reaction in asthma. Moreover, hay fever and asthma are very closely related; they are, in fact, allied conditions, and, as the symptoms in the former are generally conceded to be due to transient localized edema of the mucous membrane, it is reasonable to assume that the same explanation applies to symptoms in the latter as well.

Before dismissing the bronchoconstriction view it should be stated that since the bronchi are hollow passages, encircled by muscle, it is certainly conceivable that in consequence of the antigen-antibody reaction or some highly irritative agent on the mucous membrane the muscles are stimulated to contract. Ratner contends that the abrupt cessation of bronchial asthma after intravenous epinephrine favors the broncho constriction view.

Autopsy findings in fatal asthma indicate that although thickening of the bronchial muscles is present in some cases, heightened secretion of mucous in the bronchial walls and the occlusion of many terminal and respiratory bronchi by plugs of tough and sticky mucous are more commonly observed. Rackemann and Unger agree that death from asthma is due to thick tenacious plugs, the remains probably of both mucous and edematous fluid. Rackemann states that the mucous glands are increased both in size and in number. He considers the heightened activity of these glands to be the primary lesion.

The majority of men reporting autopsy findings place emphasis on edema of the mucous membrane, which obviously causes narrowing of the respiratory passages and further contributes to the obstruction by fluid formation. Walzer agrees that edema alone can account for the dyspnea of asthma.

Other post mortem findings are: (1) voluminous and distended lungs, (2) areas of emphysema interspersed among regions of local atelectasis and normal tissue, (3) thickened and hyalinization of the basement membrane. Significant are the findings of Hilding that ciliary action of chronic asthmatics is lost, thereby explaining the inability to expell secretions.

It is not difficult to account for the emphysematous condition or for the labored expiration of the asthmatic. During inspiration the intrathoracic pressure diminishes, permitting the bronchi to dilate. The flow of air through these passages is normally enhanced during this phase. During expiration, however, the negative pressure is reduced and all thin walled structures in the chest tend to become smaller; in the asthmatic state, the bronchioles with their reduced diameter offer a greater than normal resistance to the air and a "flutter valve" action is established. Consequently, reserve air is increased and the lungs tend to remain in a distended condition. Mucous, too, according to Rackemann, can act as a ball valve to trap the inspired air and so to increase the emphysema.

The recent work of Barach indicates that the initial obstruction during an asthma attack has a deleterious effect on the respiratory and terminal bronchi and thus on the respiratory function. This worker has shown that prolonged dyspnea in dogs made to breathe through a restricted orifice, simulating the obstruction in asthma, produces congestion and edema of the lung with areas of emphysema at the periphery. These changes are due to a greatly increased negative pressure within the chest which affects primarily the bronchial mucous membrane, leading to its swelling. When inspiration is allowed to be free and tracheal constriction is created during expiration, the changes just described do not take place and animals remain in good condition for many hours. The conclusion to be drawn from such studies, which have been amply confirmed, is that heightened negative pressure within the lungs during

the inspiratory phase of the respiratory cycle is a critical pathogenic factor responsible for lung damage and a contributing factor to further obstruction. Thus a vicious cycle is created. Barach states, too, that expiration in obstructive dyspnea increases the pressure on the pulmonary capillaries to such an extent that rupture of these vessels frequently occurs. This worker emphasizes the importance of giving drugs to lower the negative pressure in order to prevent pathological changes in the alveoli and respiratory bronchi.

B. The Mechanism of Bronchial Obstruction

There is a mass of converging evidence to substantiate the histamine concept of bronchial obstruction in asthma. Few chemical constituents of the body have such a diversity of action as histamine; few are as active pharmacologically as this amine. Histamine constricts the smooth muscles of the bronchioles; it stimulates most glands including those of the bronchi; it dilates blood vessels and increases permeability, thereby favoring edema. Histamine produces most of the symptoms of experimental asthma.

The properties of histamine important from the point of view of the present discussion are summarized in Table 1. A group of such actions may combine to produce well-known symptom complexes. In the lungs, for example, histamine, acting on the smooth muscle to produce bronchiolar constriction,

Table 1

Properties of histamine

Site of action	*Effect produced*	*Organs affected*
Smooth muscle	Contraction	Bronchiolar, vascular, intestinal and uterine smooth muscle
Capillaries	Dilatation and increased permeability	Skin, mucous membranes
Glands of external secretion	Secretagogue	Lacrimal, nasal, pulmonary and digestive glands
Cutaneous endings of pain nerves	Pain	Skin

on capillaries to produce edema and on mucous glands to produce mucous, could easily reproduce the symptoms of asthma. Likewise, in skin the urticaria and wheals of an acute reaction may be duplicated by an injection of histamine. It was this type of consideration which led Dale and Laidlaw to point out in their original paper the similarity between the phenomena of anaphylactic shock and the physiologic properties of histamine.

Most workers agree that there are no major inconsistencies to the assumption that the fundamental allergic reaction is identical with that of the anaphylactic reaction and that histamine, as one of the by-products of this reaction, is causally related to most of the phenomena. Many of the factors and idiosyncrasies of the anaphylactic syndrome remain unexplained and attempts to influence this condition of hypersensitivity by neutralizing the effects of histamine (as by creating refractoriness with increasing doses of histamine itself, by histaminase or by antihistamine drugs) have given inclusive results. It also appears clear that the cellular discharge of histamine does not account for all the phenomena of anaphylaxis. For example, proof has been presented by Jacques and Waters that a similar discharge of heparin occurs which accounts for the incoagulability of blood during anaphylactic shock. Nevertheless, the question of the involvement of the chemical is progressing from suspicion and circumstantial evidence to more direct and convincing proof that it plays the fundamental role in the anaphylactic reaction. The majority of workers seem to agree now that the source of the histamine is in the tissues of the sensitized animal and that it is released into the blood and lymph as a consequence of the antigen-antibody reaction initiated by recontact with the antigen.

Cerqua found a marked increase in blood histamine following an attack of bronchial asthma; so did Parrot, Capuani and others. Randolph and Rackemann reported an average of 45 gamma of the compound per 100 cc. of blood in 20 normal individuals with a range of variation from 19–71 gamma per 100 cc. There was a definite increase of the histamine content of nine patients with bronchial asthma during the development of symptoms, compared with levels found between attacks. Rose

also studied the variation of the histamine content of the blood in 80 patients with asthma, urticaria, hay fever and other allergic conditions. In contrast with what occurs in the normal individuals, the histamine level in allergic patients shows enormous fluctuations in the course of many months or years. Despite the fact that variations occasionally bear no relationship to the development of symptoms, they show a marked degree of instability, contrasting with the striking constancy of blood histamine in normal individuals.

It is possible that the occasional discordant results described by some workers on the estimation of histamine in the blood of allergic patients may be due to its transient nature in the blood stream. The findings appear to justify the conclusions that blood histamine of allergic individuals is considerably more labile than that of the normal and that the liberation of the chemical is frequently associated with the onset of allergic symptoms.

Evidence of a more definite nature for the release of the amine during the anaphylactoid reaction was shown by Katz and Cohen. Using heparinized blood collected from patients with pollen and dust allergies, these observers found a definite shift of the compound from the blood cells to the plasma when extracts of the assulting allergens were added. The magnitude of increase ranged from a minimum of 60–76 per cent in some cases to 168–900 per cent in most cases. Katz, using a cleverly devised method, has recently shown that histamine is liberated from the skin of allergic individuals when extracts of the offending allergen enter in contact with the lower layers of the skin. Mention should also be made of the recent findings of Kerr and his associates who found histamine or a histamine-like substance in the nasal secretion of patients with hay fever. There is thus a growing conviction that the symptoms of asthma and other allergic conditions are initiated by the liberation of histamine during the allergic state. Dragstedt, Rocha e Silva, Cohen, Cecil, Horton and others subscribe to this view.

Walzer has stated that there is little justification for the belief that every type of asthma is necessarily based upon an immunological reaction. Proof for such an assumption is still lacking in those cases in which paroxysms are precipitated by

acute infection, physical agents, organic pulmonary disease, menstruation, psychic disturbances and similar causes. Cecil also states that although allergy is an important cause of asthma, it is not the only cause. It seems highly probable that most, if not all, of these processes produce dyspnea through nonimmunologic means.

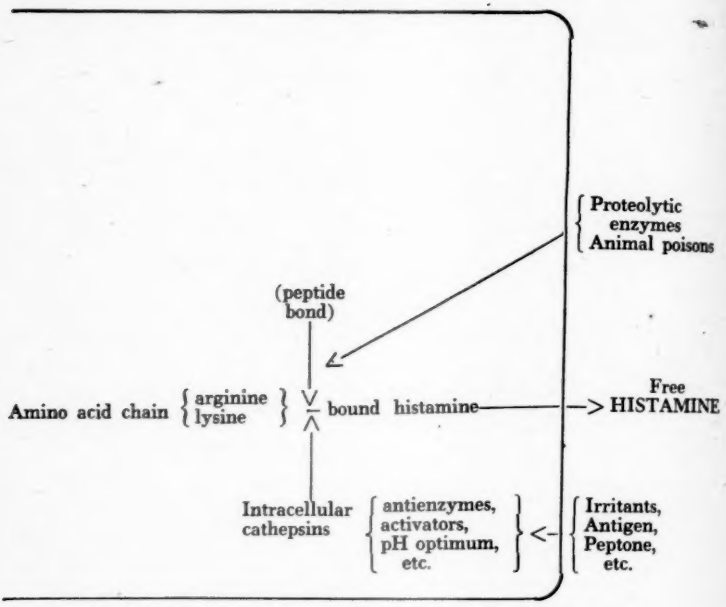
The histamine theory is particularly interesting here because the same mechanism can be invoked by a variety of agents other than allergens.

C. Present Concept of the Release of Histamine

The very attractive view of Rocha e Silva regarding the liberation of the histamine is finding favor with many students of allergy. According to this view, histamine is bound or anchored to the protoplasmic constituents of the cell by forming peptide bonds with the amino acid chain of tissue proteins. Rocha e Silva believes that the peptide bond displays a definite specificity toward proteolytic enzymes of the benzoyl-1. arginine amide type. It is further suggested that most of the histamine present in living cells is bound to arginine or to lysine and that it can be liberated by the action of a ferment displaying the specificity of trypsin. A proteolytic enzyme of the cathepsin system, probably cathepsin II, is considered the most likely enzyme to liberate histamine. This assumption is based on the findings of Fruton, Irving and Bergmann that the specific substrate for cathepsin II is benzoyl-1. arginine-amide or benzoyl-1. lysin-amide.

On this basis, Rocha e Silva has proposed an interesting theory on the chain of events involved in the liberation of bound histamine from the cell. Two distinct groups of histamine liberating substances are postulated: (1) substances which act indirectly through the endogenous cell enzymes, the cathepsins, and (2) substances such as proteolytic enzymes and animal toxins which act directly by rupturing the peptide linkages of histamine and the amino acids of cell proteins. In accordance with this view, a host of chemical and physical agents might bring about a release of histamine by activation of the cathepsins. How such agents do this is not, of course, known.

FIGURE 1



The chain reactions which might be involved in the process of histamine liberation. (From Rocha e Silva.)

It is suggested, however, that changes in pH or in concentration of hypothetical antienzymes and activators might accomplish this.

D. Antihistamine Drugs

While the circumstantial evidence for the implication of histamine in most allergic states mounts, the disappointing results with the antihistamine drugs (benadryl and pyribenzamine) in asthma have led some observers to question whether the symptoms of this condition are due solely to histamine. Most published reports have indicated that good results with these drugs in asthma (for both the perennial and seasonal types) are obtained in only 20 to 50% of the cases; a few reports

give higher figures. It is further agreed that these drugs are almost entirely without effect when the asthma is precipitated or complicated by respiratory infection.

It is difficult to explain why benadryl and related drugs control most allergic conditions better than asthma. Since lung tissue is one of the richest sources of histamine, it is possible that in asthma the histamine release is of an amount too great to be affected by ordinary tolerated doses of the drug antagonist. The failure of oral administration, then, to influence materially asthmatic cases may be the result of insufficient drug reaching the site of action. But factors other than histamine may account for the ineffectiveness of the antihistamine drugs in asthma. As previously stated, histamine may not be the only factor involved in anaphylaxis and allergy.

The mode of action of benadryl and pyribenzamine is not entirely known. Presumably the clinical results could be brought about by one or more of the following mechanisms: (1) by opposing the pharmacologic action of histamine through stimulation of the sympathomimetic system as in the case of epinephrine; (2) by direct relaxation of the bronchial musculature; (3) by preventing the release of histamine; (4) by direct chemical combination and neutralization of histamine introduced or liberated at the site of action; and (5) by blocking the action of histamine. Halpern believes they do not prevent the liberation of histamine or increase its destruction but that they modify the reaction of the organs in such a way that histamine is incapable of exercising its customary effect. Wells and his associates have shown that benadryl does not prevent the release of histamine during anaphylactic shock in dogs. These workers believe that the mode of action is most likely a competition between histamine and the drug for a given site of action.

Code very wisely warns that although the effects of these drugs are certainly associated with histamine, they may not be exclusively so. The fact that a drug relieves symptoms of certain allergic diseases, which can for the most part be duplicated by injected histamine, is not conclusive proof that such symptoms are due to histamine. He nevertheless states: "For

the present it is clear, however, that benadryl and similar compounds are drawing together a widely diversified group of clinical conditions whose common denominator seems likely to be some abnormality of histamine metabolism."

Of the possible methods of avoiding, reducing, tolerating or counteracting histamine and allergic reactions, it is premature to preduce which will have the greatest value. Continued search for antihistamine drugs is most important. Such drugs should be helpful in elucidating many unsolved physiological problems, and their clinical usefulness can hardly be overstated.

From the probable mode of action of these drugs it becomes quite evident that they can act only as palliative agents, and do not eliminate the basic mechanism responsible for the allergic disorder. As Friedlaender has pointed out, their use in no way diminishes the importance of careful search for etiologic factors in order that they may be eliminated where possible, or of measures taken to increase the individual's immunity where removal from the environment is not feasible.

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THE ORAL TRANSMISSION OF MURINE TYPHUS IN HUMANS*

MORRIS POLLARD, D. J. WILSON, H. R. LIVESAY, AND J. C. WOODLAND

The transmission of murine typhus by arthropods has been demonstrated so frequently that one may consider this as the principal method of transmission from mammal to mammal. Many reports have demonstrated that this disease can be transmitted experimentally in mammals through infestation with infected fleas *(Xenopsylla cheopsis)* and mites *Liponyssus bacoti;* and cases of the disease in humans are frequently associated with exposure to such arthropods. The disease has been induced in mammals through the respiratory tract, by Castenada with such success that the resulting infected lungs are considered suitable either for vaccine or for complement fixing antigen.

The possibility of acquiring typhus infection through the alimentary tract has caused some controversy among epidemiologists and typhus control personnel. Violle and Suntel offered experimental data on attempts to induce murine typhus infection in animals through their alimentary tracts. Nicolle *et al.* report that eight monkeys were fed infected brain emulsions and that four of these were immune when challenged with typhus. It should be pointed out, however, that precautions were not taken against a possible inhalation of the agent, and that no actual case of the disease developed with the ingested material.

Since murine typhus has a reasonably low fatality rate in young humans, it was considered more direct and conclusive to attempt the oral transmission of this disease with human volunteers.

EXPERIMENTAL

Six young healthy male volunteers were selected for the feeding experiment. They were questioned at length concern-

*From the Eighth Service Command Laboratory, Fort Sam Houston, Texas. Received for publication July 6, 1946.

ing previous illnesses and none professed any history suggestive of an arthropod-borne disease. Their serums were examined prior to the experiment and all were found to be negative for typhus by the complement fixation test and negative for significant Proteus OX19 agglutination titers.

The infected food was in the form of chick embryo yolk sacs which were infected with the Wilmington strain of murine typhus. Cases I, II, and III were fed infected yolk sac material which was collected on the same day (Pool 1010). Cases IV, V, and VI were fed infected yolk sac material which had been stored in the dry ice chamber for four days (Pool 1005). The infectious material was transmitted in a dry ice chamber to an institution located two hundred miles from the laboratory.

Just prior to the feeding the infected yolk sacs were emulsified in saline and were transferred to gelatin capsules (no. 00) with a syringe and needle. The filled closed capsules were carried to an adjoining room and placed into the mouth of the volunteer. Four cc. of the material was thus swallowed with tap water and the men were subsequently observed, to preclude the possibility of regurgitation. The feeding experiment was performed four hours following lunch and two hours prior to the following meal. All six of the volunteers were then isolated in a separate room of the institutional hospital and were observed at least three times daily during the succeeding four weeks. A serum specimen was collected from each volunteer at five-day intervals. Each specimen was examined for typhus complement-fixing antibodies and for Proteus OX19 agglutinins.

After the volunteers had eaten the test materials, 2.0 cc. of the yolk sac material from each lot was injected intraperitoneally into four guinea pigs and the material was also passaged into additional chick embryos. This material was also examined for bacterial organisms with thioglycollate broth and blood agar plates.

Results

Subsequent clinical and serological examinations of cases I, II, III, IV, and V failed to reveal any evidence of typhus

infection as a result of the feeding experiment. All individuals remained normal.

Eleven days after the feeding experiment Case VI suddenly developed a severe headache, generalized malaise, and insomnia. A generalized maculo-papular rash developed on the fourth day of illness and was evident for six days thereafter. A febrile temperature was recorded for eleven days and defervescence came by crisis (Chart I). Sedatives were adminis-

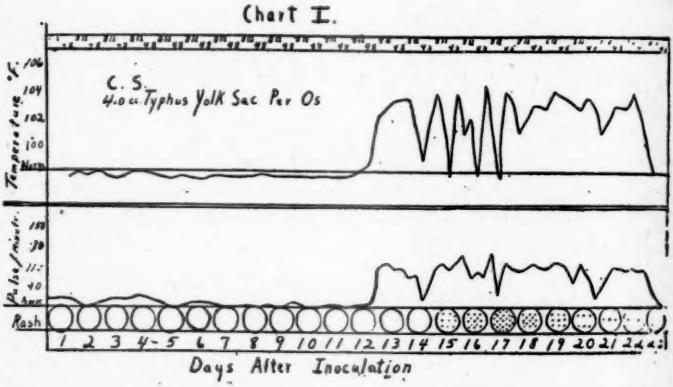

Chart I. Temperature, pulse and skin rash of experimental typhus fever volunteer number VI.

tered early in the course of the disease and may explain the vacillations in temperature. No alteration in blood count could be detected during the course of the disease. This volunteer developed a typical clinical infection of typhus fever; and serological examinations demonstrated rising titers for Proteus OX19 agglutinins and for typhus complement-fixing antibodies, the latter attaining a peak titer of 1:2560 (Chart II).

The control guinea pigs developed typical febrile reactions and orchitis (Chart III). The short incubation period is observed frequently with yolk sac inoculums. All developed complement fixing antibodies for typhus.

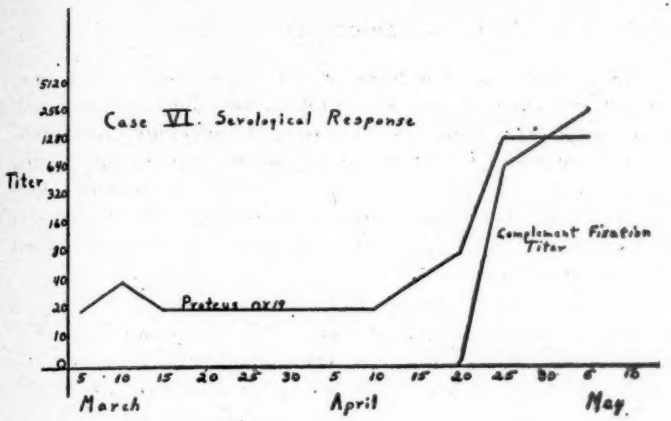

Chart II.

Chart II. The serological reaction for typhus fever as manifested by volunteer number VI.

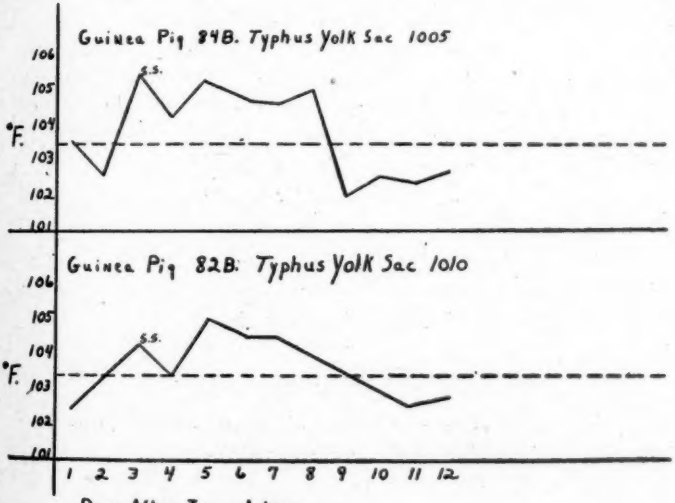

Chart III.

Chart III. Febrile reactions of typhus fever inoculated control guinea pigs.

Discussion

We realize that flea feces or rat urine would be a more probable source of natural human infection; however, we were interested primarily in having a sufficient quantity of virulent material for all phases of control inoculations for the experiment, therefore, we had to resort to infected chick embryo yolk sacs. The dosage administered to the volunteers was probably very large in comparison with possible natural dosage by mouth.

One man out of six developed typhus fever as a result of eating typhus contaminated food. This individual (Case VI) was questioned rather extensively regarding any gastro-intestinal symptoms which might be referable to a lesion through which the agent possibly gained admission to the body. No evidence which might be adduced to such a lesion could be elicited. Whatever peculiarity this man had which might have made him susceptible, the fact remains that an individual, who was considered clinically normal, contracted the disease by way of the digestive tract. The institution at which this experiment was conducted was a newly constructed modern building in which there had been no history of typhus among the inmates. All of the volunteers had been in this institution at least three months prior to this experiment.

It may be possible that certain naturally-occurring cases of murine typhus developed as a result of consuming food contaminated either with infected urine or flea feces. This might explain certain cases of the disease where direct exposure to a focus of infection is uncertain.

Conclusion

One human volunteer of six acquired an active typhus fever infection by ingestion of typhus infected food.

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ANTAGONISM OF THE DIABETOGENIC ACTION OF ALLOXAN BY PENTNUCLEOTIDE IN THE RAT*

G. A. Emerson, P. L. Ewing, and Thurlo B. Thomas†

Since the demonstration of chemical nesidiectomy by alloxan (Shaw Dunn, Sheehan, and McLetchie, 1943), its mechanism has been controversial. The biochemorphic approach has been exploited to the extent of testing many agents sharing structural similarities, for their diabetogenic action (Thorogood, 1944; Goldner and Gomori, 1944) or initial hypoglycemic effect (Jacobs, 1937). Methylalloxan (Hidy, 1946; Brückmann and Wertheimer, 1945) and 2-(*p*-acetylaminostyryl)-6-dimethylaminoquinoline methochloride (Shaw Dunn, Sheehan, and McLetchie, 1943) exhibit comparable destructive effects on β-cells of the islets of Langerhans. Dialuric acid may be diabetogenic in large dose (Brückmann and Wertheimer, 1945) but is without action in moderate dose (Goldner and Gomori, 1944; Jacobs, 1937); its effect is considered due to alloxan present as a contaminant through eremacausis before injection (Lazarow, 1946). Brückmann and Wertheimer also report alloxantin, dimethylalloxantin and methyldialuric acid as diabetogenic on intravenous administration to rats. No generally applicable theory of the relation of chemical structure to diabetogenic action has emerged from these data.

Valid evidence of mechanism of action may be obtained indirectly, through observation of chemical relations of agents antagonizing the effect in question. Substances incompatible with alloxan *in vitro*, or which interfere with certain of its reactions, have been tested (Weinglass et al., 1945); among 18 compounds tested, only 3,4-diaminotoluene, *o*-phenylenediamine and $NaHSO_3$ were active in inhibiting the diabetogenic action, but these 3 agents were effective in approximately a 1:1 molar ratio. Despite previous reports of lack of inhibitory

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effect of large doses of glutathione (Leech and Bailey, 1945) and cysteine (Weinglass et al., 1945), still larger doses of these sulfhydryl compounds were found to prevent alloxan diabetes (Lazarow, 1946). Thioglycolic acid has a similar action, while many reducing agents lacking the –SH group do not. The sulfhydryl compounds were effective in a molar ratio of 8–30:1 when administered 1–2 minutes prior to alloxan, but gave only partial protection when injected within 3 minutes after alloxan. Alloxan is apparently converted by –SH compounds to nondiabetogenic congeners when incubated several hours with human or rabbit plasma (Leech and Bailey, 1945). When the pancreatic duct is ligated, alloxan does not cause diabetes (Walpole and Innes, 1946).

Rats starved 48–60 hours are much more susceptible to alloxan diabetes than are normal, fed rats (Kass and Waisbren, 1945). Glucose reduces the susceptibility of fasted rats to alloxan if given 6 hours before alloxan, but not if given 1 hour before alloxan. Epinephrine, given intraperitoneally immediately before alloxan is injected subcutaneously, prevents its diabetogenic action. The tentative explanation offered, that these procedures affect susceptibility by influencing adrenal cortical activity since there is no correlation with blood sugar level at the time of treatment with alloxan, is untenable for epinephrine inasmuch as the strong splanchnic vasoconstriction produced by its intraperitoneal injection would effectively minimize the diabetogenic action by allowing more complete detoxication of the alloxan before it could reach the pancreas. In view of a molar ratio of about 1:400 (epinephrine:alloxan), it is also unlikely that epinephrine acts in a chemical way to inhibit the alloxan effect.

The many examples of antagonism of diverse pharmacologic effects by compounds closely allied structurally to the effective agent suggest that a more potent antagonist to alloxan than any of the substances hitherto examined might be found among the pyrimidines themselves, or closely related ureides and hydantoins. If one assumes that alloxan has a direct effect on the pancreas, it should be recognized that the actual mass of the agent reaching and acting upon the islet cells approaches

the infinitesimal; the mass of alloxan necessary to destroy most of the β-cells in the pancreas of a rat has been estimated (Lazarow, 1946) conservatively to be much less than 10 γ. Diabetogenesis in the rat thus involves a mass of alloxan of the order of 10^{-8} *M*, acting for less than 2–3 minutes. Actions of other agents acting in the same magnitude are ordinarily dependent upon receptive mechanisms in the cells involved in the response, or upon active patches on cell membranes. In such actions, effective antagonism by agents closely related chemically is considered a result of competitive affinities for the receptors.

As a preliminary to a comprehensive examination of homologues of alloxan, the inhibition of alloxan diabetes by a mixture of pentose nucleotides was studied. The influence of time and route of administration, and dosage, is reported here.

Methods

Fifty-nine adult white rats were divided into 4 series, fasted 36–72 hours, and injected intravenously with 40 mg./Kg. (0.25 m*M*/Kg.) of alloxan monohydrate, according to a technique designed to produce diabetes in all rats (Lazarow, 1946). For greater certainty of quantitative administration, injection of a 4% solution in 0.5% NaCl was made through a 30G needle into the superficial veins of the thigh, which are easily visualized, rather than more or less blindly into the tail veins. Rats were neither heated nor anesthetized before injection. Substances in the blood reducing alkaline ferricyanide, representing "blood sugar," were estimated (Hagedorn and Jensen, 1923) at appropriate intervals before and after injection of alloxan, on blood samples obtained from the tail, or, occasionally, by cardiac puncture.

In the first series, 3 rats were given intraperitoneally 350 mg./Kg. of pentose nucleotides obtained from yeast nucleic acid, as 5 ml./Kg. pentnucleotide N. N. R. The injection of nucleotides was made 30–45 minutes before treatment with alloxan, 72 hours after beginning the fast. Another 3 rats received mg./Kg. $ZnSO_4 \cdot 7H_2O$ intramuscularly about 30 minutes before alloxan; since their blood sugar responses did not differ from those of

3 rats given alloxan without other treatment, they are included with the latter as illustrating the effect of alloxan (Fig. 1). All 9 rats were fed immediately following injection of alloxan.

The second series, fasted 36 hours, comprised 2 rats treated with alloxan alone, 2 given 350 mg./Kg. pentose nucleotides intramuscularly 30 minutes before alloxan, 2 given the same dose of nucleotides intramuscularly 30 minutes after alloxan, 2 treated intragastrically with 700 mg./Kg. nucleotides 30 minutes before alloxan, 2 treated similarly 30 minutes after alloxan, 2 given 70 mg./Kg. nucleotides intraperitoneally 30 minutes before alloxan, and 2 treated similarly but given also 20 mg./Kg. $ZnSO_4 \cdot 7H_2O$ intramuscularly at the same time, 30 minutes before alloxan. Food was made available to these 14 rats immediately after injection of alloxan.

The third series included 8 rats given alloxan alone after a 48-hour fast, 2 given 350 mg./Kg. nucleotides intraperitoneally 30 minutes before alloxan, 2 treated similarly 2 hours before alloxan, 2 treated similarly 24 hours before alloxan, 2 given the same dose of nucleotides intravenously 30 minutes before alloxan, and 2 treated similarly by vein 2 hours before alloxan. All 18 were fed immediately after treatment with alloxan. One of the 8 rats given alloxan alone was treated with 0.5 g./Kg. glucose intravenously about 30 minutes after alloxan and apparently recovered from a semicomatose, convulsive state, but refused to eat and died within 84 hours, with a loss of body weight of 12%; on necropsy, bilateral hydronephrosis and a bladder distended with red urine were noted. Pancreatic tissue was unusually scanty in this rat. Despite the lack of a typical hyperglycemic response, the blood sugar was increased to 242 mg.% in this rat 40 hours after alloxan, as compared with an average of 455 mg.% for the other 7 rats at this time. Therapy with glucose in this instance cannot be considered protective in the sense in which pre-treatment with glucose has been reported to inhibit alloxan diabetes (Kass and Waisbren, 1945).

In the fourth series, fasted 40 hours before treatment, 9 rats were given alloxan alone, 3 received 350 mg./Kg. of nucleotides intraperitoneally 1 hour before alloxan, and 3 received

the same dose of nucleotides intravenously 1 hour before alloxan. In addition, a rat was treated with 350 mg./Kg. nucleotides intravenously and 2 were given the same dose of nucleotides intraperitoneally, without alloxan treatment. These 3 rats were not fed until 4 hours after receiving the nucleotides, and the 15 others were fasted 4 hours after injection of alloxan; *i.e.*, all 18 were fasted for 44 hours.

One additional rat in the first series and 2 in the second series were discarded due to apparent ill-health during the pre-treatment period or death within 8 hours after treatment with alloxan. None of these 3 received nucleotides. Organs of the remaining 59 were examined grossly after death from the effects of alloxan or by a blow on the head; as noted in the figures, most of the rats in the last 2 series survived the period of observation, while several were killed at intervals before conclusion of observations in the first 2 series. No lesions were found in those dying from effects of alloxan which could be considered significantly contributory as a cause of death, except in the instance of the rat which received glucose. Mild pulmonary congestion was occasionally observed, particularly in the first 2 series. Water intake was excessive in the diabetic rats and a distended bladder was a common finding. Occasionally the urine was tinged smoky red, but this was marked in only one rat other than the rat which received glucose. This coloration is more probably due to excretion of murexide or other chromogenic derivatives of alloxan than to hematuria. Bright red staining of portions of the kidney, particularly about the medullary rays, was noted in many of the rats. The pancreas, adrenals, thyroid glands, thymus and pituitary, and portions of the liver, spleen, kidney, testis and lung were fixed in Helly's fluid, washed, treated with 50% dioxane and dioxane–I_2, and preserved in dioxane for cytologic study to be reported later by one of us (T. B. T.).

Results

Effects of the various treatments noted above upon the blood sugar levels are presented in the accompanying figures. Figure 1 illustrates that all of 6 rats became diabetic after treatment with alloxan alone or alloxan given after pre-treatment with

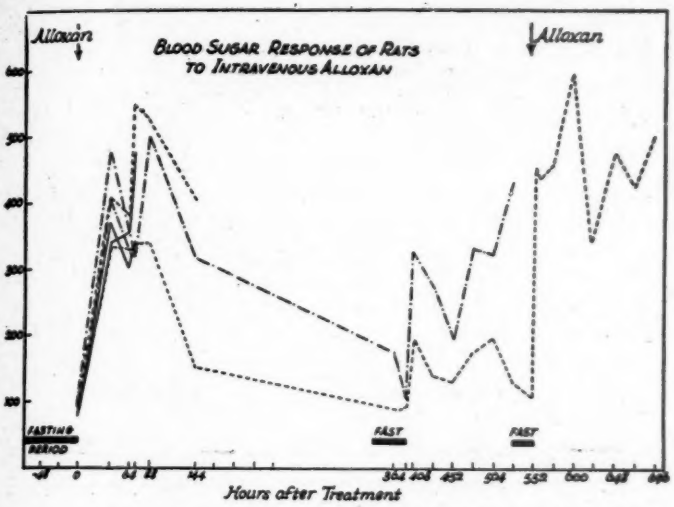

Figure 1. Blood sugar responses of 6 rats treated with 40 mg./Kg. alloxan monohydrate intravenously after a 72-hour fast (3 pre-treated with $ZnSO_4$; see text). A second injection of alloxan was given to 1 rat on the 23d day.

$ZnSO_4$. One of the rats treated with alloxan alone later showed normal blood sugar levels on fasting, 16 days after treatment; it was given a second intravenous injection of 40 mg./Kg. alloxan monohydrate after a 24-hour fast on the 23d day following the first treatment, whereupon it became severely diabetic and progressively cachectic until the 29th day, when it was killed.

In figure 2, it is shown that none of 3 rats became diabetic after receiving the same amount of alloxan following intraperitoneal injection of nucleotides 30–45 minutes previously, in a dose of 350 mg./Kg. On the 23d day after treatment, and following a 24-hour fast, one of these rats was treated with 40 mg./Kg. alloxan monohydrate alone and became severely diabetic, dying within 4 days.

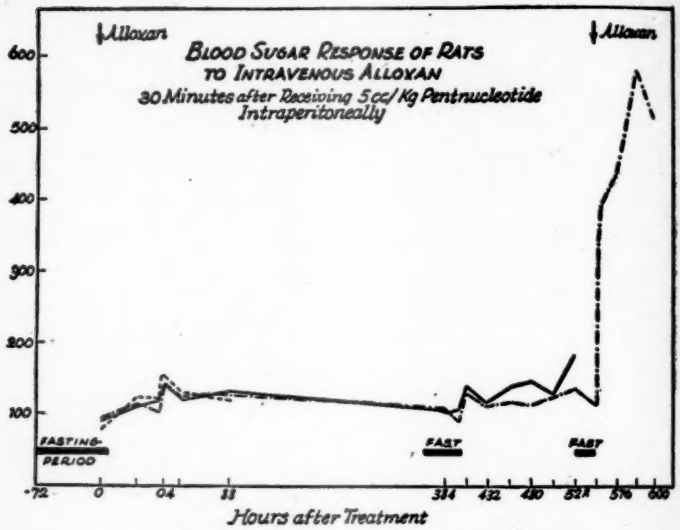

Figure 2. Blood sugar responses of 3 rats to 40 mg./Kg. alloxan monohydrate given intravenously 30 minutes after 350 mg./Kg. nucleotides intraperitoneally. One rat received a second injection of alloxan on the 23d day, without-pre-treatment with nucleotides.

Figure 3a demonstrates the relative ineffectiveness of nucleotides given intramuscularly. Two rats given alloxan alone became diabetic, while one became diabetic in each of the groups of 2 given nucleotides intramuscularly before or after alloxan, respectively. Figure 3b shows the complete ineffectiveness of large doses of nucleotides given orally 30 minutes before or after alloxan, and of small doses of nucleotides given intraperitoneally as a pre-treatment.

Figure 4 establishes further the uniform diabetogenic action of alloxan given intravenously. The lower, dotted line represents the blood sugar response in a rat treated with glucose intravenously 30 minutes after alloxan; the lack of a more striking hyperglycemia is probably due to anorexia, as this rat died in 84 hours, with cachexia.

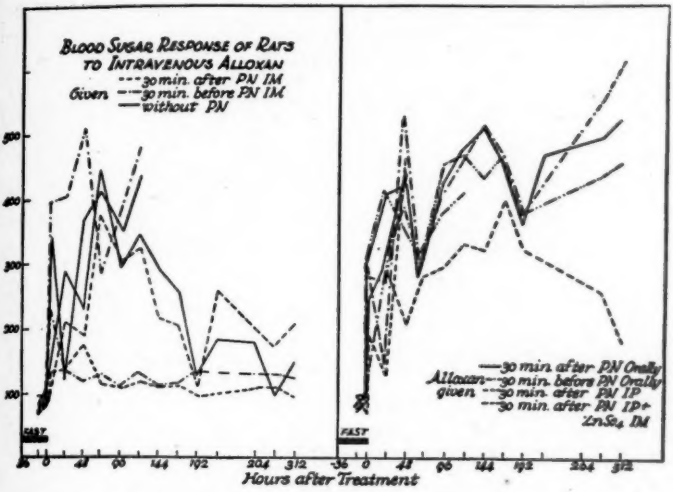

Figure 3a, left. Blood sugar responses of 2 rats given 40 mg./Kg. alloxan monohydrate intravenously, and 2 groups of 2 rats given the same treatment 30 minutes before or after, respectively, receiving 350 mg./Kg. nucleotides intramuscularly.

Figure 3b, right. Blood sugar responses of 4 groups of 2 rats given 40 mg./Kg. alloxan monohydrate intravenously: 30 minutes after receiving 700 mg./Kg. nucleotides orally; 30 minutes before similar treatment; 30 minutes after receiving 70 mg./Kg. nucleotides intraperitoneally; and 30 minutes after similar treatment plus $ZnSO_4$ intramuscularly, respectively.

Figure 5 represents the effect of time of the intraperitoneal injection of nucleotides on their protective action. When alloxan was given exactly 30 minutes after the nucleotides, one of 2 rats so treated became diabetic. When the pre-treatment interval was increased to 2 hours, neither of 2 rats became diabetic within the first few days after alloxan therapy, although one showed moderately high blood sugar levels 10–14 days later. When the pre-treatment interval was lengthened to 24 hours, the nucleotides had no apparent protective action.

Figure 6 indicates the effectiveness of intravenous pre-treatment with the nucleotides. One of 2 rats treated 30 minutes before receiving alloxan showed a sustained hyperglycemia,

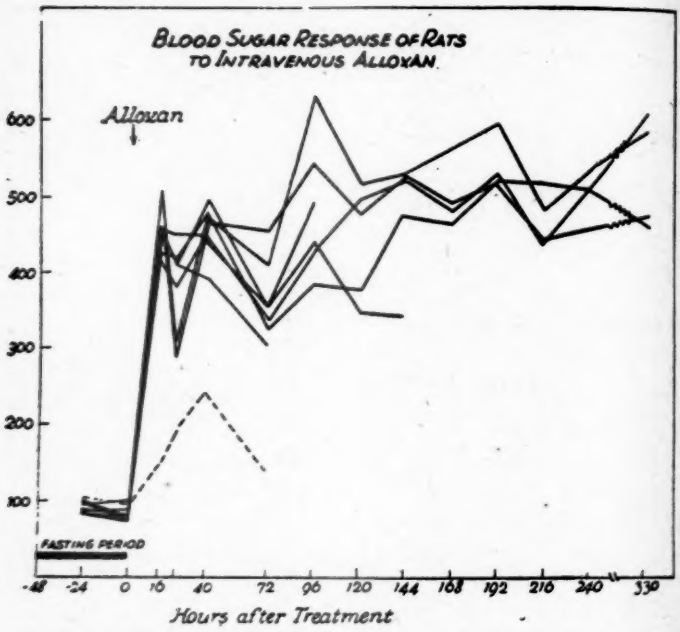

Figure 4. Blood sugar responses of 8 rats to 40 mg./Kg. alloxan monohydrate given intravenously after a 48-hour fast. The rat showing the least hyperglycemia became comatose shortly after receiving alloxan, was treated with glucose, and died in 84 hours; see text.

but another so treated and 2 pre-treated 2 hours before alloxan showed normal blood sugar levels after the first 24 hours following treatment.

Figure 7 again makes evident the certainty of development of diabetes in rats treated intravenously with alloxan alone, but also gives a more precise picture of changes occurring within the first few hours after alloxan is given. The 9 rats represented were fasted an additional 4 hours after injection of alloxan, while the 44 whose treatments are described above were fed immediately upon receiving alloxan. Although a marked hypoglycemia was expected after a brief initial hyper-

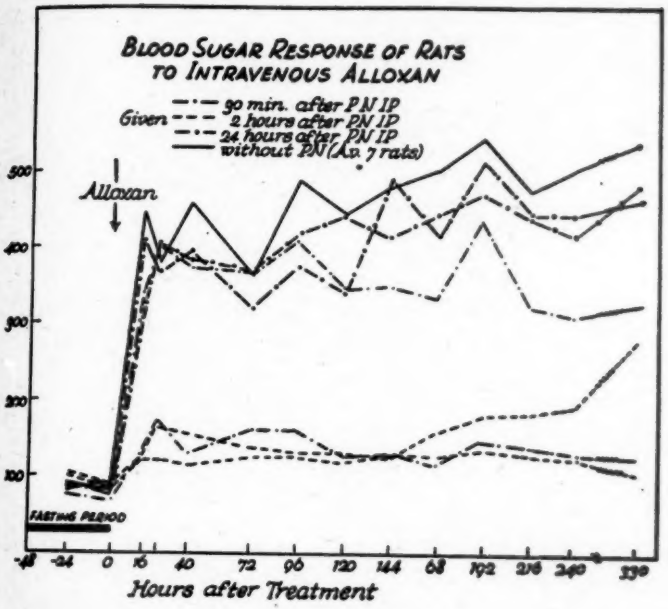

Figure 5. Blood sugar responses of 6 rats to 40 mg./Kg. alloxan monohydrate given intravenously at various time intervals after intraperitoneal injection of 350 mg./Kg. nucleotides.

glycemia, only 2 of the 9 showed blood sugar levels at the end of the post-treatment fast which were below those found before injection of alloxan. Considerable variation is recognized in the time relations of the response to alloxan, and the present lack of a strong hypoglycemic response is best interpreted as due to the brief interval of fasting after treatment. Two hours after feeding, all but 3 showed diabetic levels of blood sugar.

Figure 8 reveals the protective effect of nucleotides given intraperitoneally 1 hour before alloxan; none of 3 rats became diabetic. Figure 9 indicates that the same dose of nucleotides is not as effective when given intravenously 1 hour before

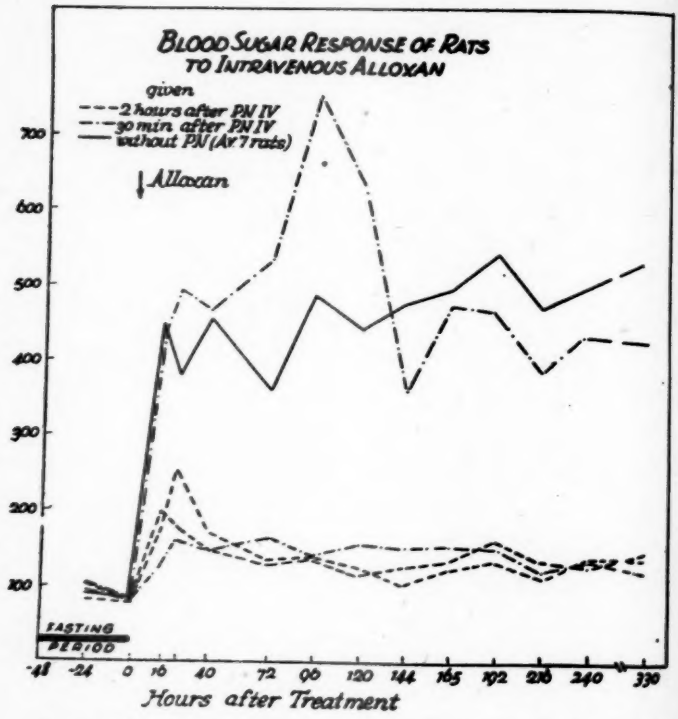

Figure 6. Blood sugar responses of 4 rats to 40 mg./Kg. alloxan monohydrate given intravenously 0.5 or 2 hours after 350 mg./Kg. nucleotides intravenously.

alloxan. The 2 rats which developed moderately high blood sugar levels, of 3 so treated, nevertheless show a considerable delay in the hyperglycemic response, which may be taken to signify a partial, even though ultimately unsuccessful, protection.

Figure 10 portrays the blood sugar changes occurring in rats treated with nucleotides intravenously or intraperitoneally, without alloxan. The moderate increase in blood sugar content which supervenes for several hours after treatment is not followed by any persistent change from normal.

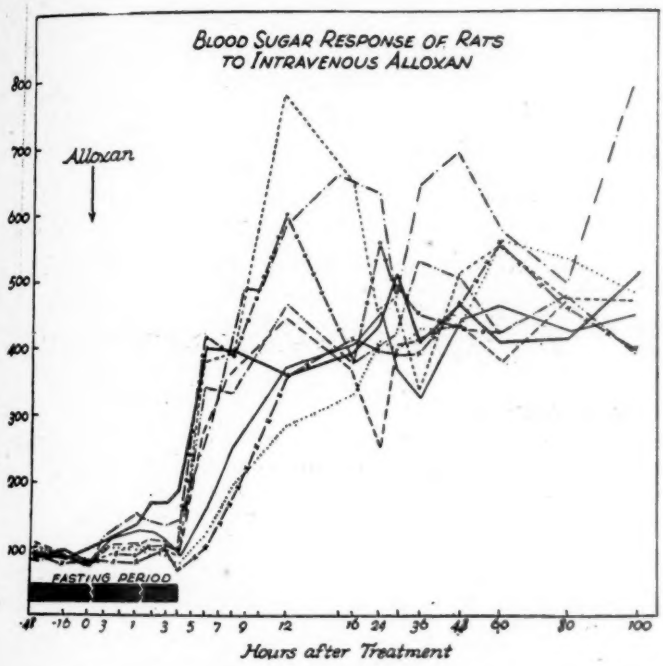

Figure 7. Blood sugar responses of 9 rats to 40 mg./Kg. alloxan monohydrate intravenously, illustrating the early effects of alloxan.

Effects on body weight.—Hédon found in 1893 that, despite excretion of some 20 g. of glucose each 24 hours, rabbits developing diabetes 20–30 days after injection of olive oil into the duct of Wirsung "ne maigrissent pas; au contraire, certains augmentent très notablement de poids et engraissent, car ils compensent et au delà leur trouble nutritif par une alimentation exagérée; ils sont polyphages et polyuriques." Similar findings are noted by Shaw Dunn and McLetchie (1943).

Excessive intake of food and water by diabetic rats in the present study was readily discernible without exact measurement, but considerable cachexia was noted in many of the rats

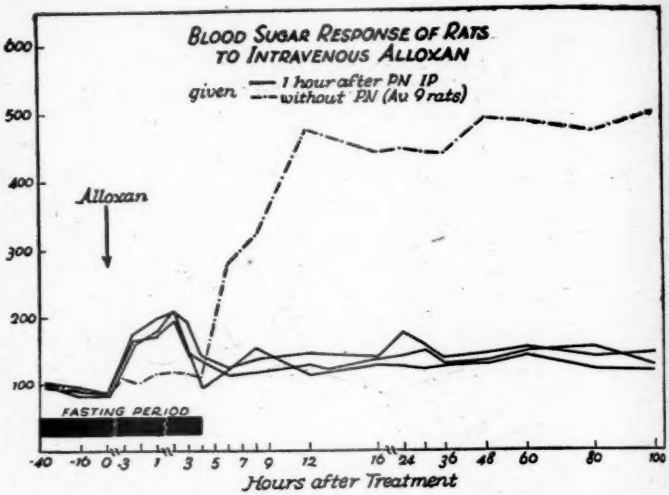

Figure 8. Blood sugar responses of 3 rats to 40 mg./Kg. alloxan monohydrate given intravenously 1 hour after 350 mg./Kg. nucleotides intraperitoneally.

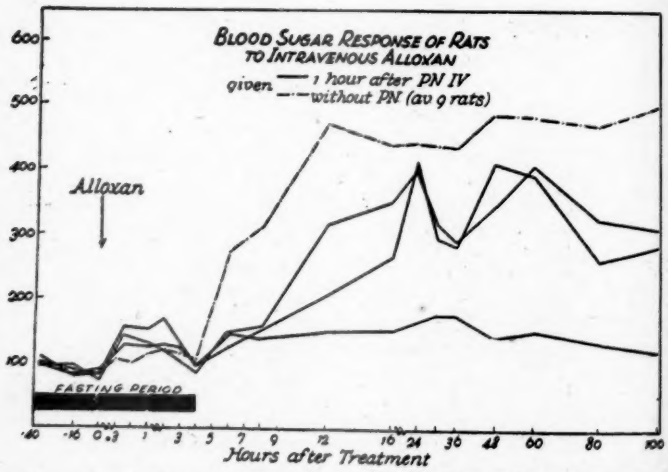

Figure 9. Blood sugar responses of 3 rats to 40 mg./Kg. alloxan monohydrate given intravenously 1 hour after 350 mg./Kg. nucleotides intravenously.

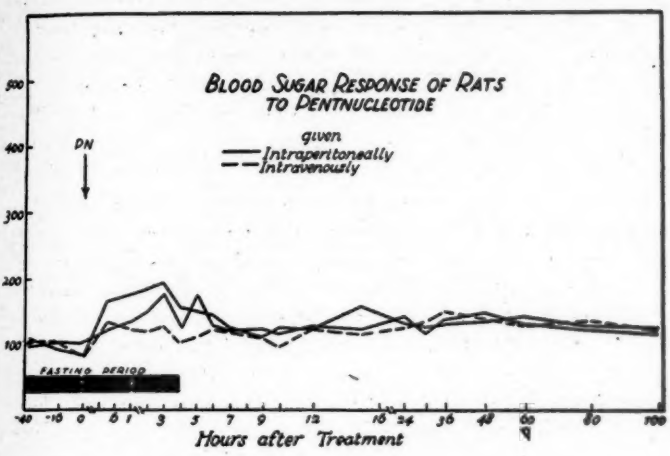

Figure 10. Blood sugar responses of 3 rats to 350 mg./Kg. nucleotides given intravenously or intraperitoneally.

at necropsy. Body weight of all rats was noted before fasting, at the time of treatment, and at intervals thereafter. While, in general, those individuals with the most severe diabetes showed also the greatest loss in weight, the following data are not considered to reflect with any precision the actual cachexia, since most of the diabetic rats had greatly distended bladders at necropsy and may have had considerable tissue hydration as well.

Data from the first 2 series are not easily summarized since many of the rats were killed before the conclusion of the observations. Those from the last 2 series may be taken as representative. In the third series, those rats treated with alloxan alone showed a weight loss of 30% (24–38%), excepting the aberrant individual dying in 84 hours. One rat protected with 350 mg./Kg. nucleotides given intraperitoneally 30 minutes before alloxan exactly maintained its weight, while another, which showed moderate diabetes after similar treatment, lost 8%. Both rats treated intraperitoneally with nucleotides 2 hours before alloxan made slight gains (2, 6%).

Those treated intraperitoneally 24 hours before alloxan showed losses of 14 and 24%. Both were diabetic. One rat developing severe diabetes after intravenous treatment with nucleotides 30 minutes before alloxan lost 17%, while a rat similarly treated, which did not become diabetic, gained 3%. Both rats given nucleotides intravenously 2 hours before alloxan showed small losses (3, 7%) although neither became diabetic.

Findings in the fourth series were similar although the time of observation was only 100 hours, less than one-third as long as in the third series. The mean weight loss for 9 rats treated with alloxan alone was 28% (21–40%). The 3 rats protected with 350 mg./Kg. of nucleotides given intraperitoneally 1 hour before alloxan had losses of 10, 8, and 10%, respectively, although none was diabetic. The three rats treated similarly with nucleotides intravenously before alloxan showed losses of 18, 10, and 16%, respectively; the first and third of these rats became moderately diabetic, but later than those treated with alloxan alone. A rat treated intravenously with nucleotides alone lost 9%, and those treated intraperitoneally, 11 and 12%, respectively.

Organ weight/body weight ratios were not estimated since specific changes were not foreseen. There was, however, a marked increase in the size of the thymus in those rats which received nucleotides, and a striking diminution in the size of the testes in rats receiving alloxan alone.

Discussion

Two characteristics of the antagonism of nucleotides to alloxan are significant in directing further pharmacodynamic study: (1) there is a definite lag period before nucleotides act, even with intravenous administration; and (2) there is a graded response, as evidenced by slower development of hyperglycemia when nucleotides fail to protect against alloxan.

In regard to the latent period, alternate hypotheses involve metabolites of nucleotides acting in a simple chemical fashion to block alloxan, or a more nonspecific effect on the pancreas, other organs, or their humoral control. The mixture of nucleotides from yeast nucleic acid consists essentially of compounds

of the purines adenine and guanine, and the pyrimidines uracil and cytosine, with *d*-ribose and phosphoric acid. Nucleotides given parenterally could either be used anabolically to form nucleic acids or catabolically to yield their components and the degradation products of these. If the antagonistic activity of phytonucleotides resides in one of the pyrimidines or purines, or in a metabolite of these, it presumably would be much greater than 4x that of the mixture, since these metabolites cannot be present in comparably large amounts in tissue after administration of nucleotides. The series of studies on metabolism of the pyrimidines (Cerecedo, 1931) and of their interactions in S metabolism is immediately pertinent to this concept. So also may be theoretical considerations (Archibald, 1945) concerning paths of metabolism of alloxan itself: to alloxanic acid, at the alkaline pH of tissues and blood; to alloxantin and dialuric acid, through reduction by sulfhydryl compounds in tissues; and to alluranic acid, by association with urea.

The possibility of an indirect or nonspecific action of nucleotides will be explored in cytologic studies now in progress, which may also contribute to a better understanding of factors involved in the graded response. Variation in susceptibility to alloxan in different species, in the same species according to body weight (Kass and Waisbren, 1945), or other factors (Shaw Dunn and McLetchie, 1943), may be related directly to some simple mensurable variant. Unpublished observations (Thomas, 1945), on effects of alloxan on the gonads and on effects of castration on alloxan susceptibility, have indicated that there is not a simple relation of the gonads, the pituitary and the pancreas in alloxan diabetes. The large variations in susceptibility in relation to body weight, time of fasting, and glucose administration (Kass and Waisbren, 1945) suggest that some relatively labile organ or function is involved; adrenal cortical activity has been considered (Kass and Waisbren, 1945), and studies are under way on effects of ablation of organs rich in nucleic acid on susceptibility of the rat to alloxan.

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Professor Hamilton H. Anderson made available the facilities of the Department of Pharmacology of the University of California for preliminary studies. The amiable coöperation of Professors Benedict E. Abreu and Carroll Handley aided greatly in the first part of the work.

SUMMARY

The antagonism of nucleotides from yeast nucleic acid (Pentnucleotide, N. N. R.) to the diabetogenic action of alloxan in the rat has been explored in regard to route of administration, time of administration, and dose of nucleotides. The antagonism is a graded response with a definite latent period.

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CALLING ATTENTION TO:

Items of Possible Interest to Friends of Our Effort

SEPTEMBER, 1946

1. BOOKS: Certain to be a Pulitzer prize biography is J. F. Fulton's *Harvey Cushing*, most carefully prepared and now ready (C. C. Thomas, Springfield, Ill., 1946, 834 pp., $5). Soon to appear is 10 vol. *Encyclopedia of Chemical Technology* with much on chemotherapy and drugs (Interscience Encyclopedia, Brooklyn, 1947). B. M. Patton offers well illustrated *Human Embryology* (Blakiston, Phila., 1946, 776 pp., 1,366 illus., $7). H. Gold edits *Cornell Conferences on Therapy* (Macmillan, N.Y., Vol. 1, 1946, 322 pp., $3.25). J. M. Nielson offers *Agnosia, Apraxia, Aphasia; Their Value in Cerebral Localization* (Hoeber, N.Y., 1946, 300 pp., $5). H. Cramer analyses *Mathematical Methods of Statistics* (Princeton Press, 1946, 570 pp., $6). New edition finally ready of classic J. Peters and D. Van Slyke: *Quantitative Clinical Chemistry* (Williams & Wilkins, Baltimore, Vol. 1, Interpretations, 1,000 pp., $7, 1946; Vol. 2, Methods, soon!). For Ether Centennial E. S. Ellis offers *Ancient Anodynes: Primitive Anesthesia*, which is quite British (Heinemann, London, 1946, 187 pp., 21s). G. Bankoff dekruifs incompletely on *The Conquest of Pain: the Story of Anesthesia* (MacDonald, London, 1946, 204 pp., 6s). F. F. Nord edits Vol. VI of *Advances in Enzymology* (Interscience, N.Y. 3, 1946, 575 pp., $6.50). R. R. Gates offers *Human Genetics* (Macmillan, N.Y. 11, 1946, 2 Vols., 1,518 pp., $15).

2. HYPERTENSION: E. Braun-Menendez & Co.'s *Renal Hypertension* is well translated by L. Dexter (C. C. Thomas, Springfield, Ill., 1946, 451 pp., $6.75). Symposium on *Experimental Hypertension* appears by H. Goldblatt, E. C. Coke, L. F. Leloir, I. H. Page, A. Grollman, G. E. Wakerlin, J. W. Remington, our E. Ogden, W. D. Collings, L. A. Sapirstein, R. J. Bing, W. Goldring, and others (Sp. Publ., N.Y. Acad. Sci., Vol. 3, 1946, 180 pp.). B. Halpert and A. Grollman find merely cardiac hypertrophy and renal lesions after 8 months' chronic hypertension from renal ligatures in rats (*Proc. Soc. Exp. Biol. Med.*, 62:273, 1946).

3. A. C. S.: More information arrives in English summary on Bogomolets' antireticular cytotoxic serum: P. D. Marchuk discusses methods of preparation and tests for appropriate dosage (*Med. J. Acad. Sci. Ukranian S.S.R., Inst. Clin. Physiol.*, 14:273, 1945). E. A. Tatarinov describes dermal test reaction to trypan blue under influence of A.C.S. (*ibid.*, p. 81). He also offers notes on factors of body resistance to tumor growth (*ibid.*, p. 50). L. N. Mashkilleison discusses A.C.S. in chronic skin ulcers (*Am. Rev. Sov. Med.*, 3:433, 1946).

4. LATE IN ARRIVING, STILL NOTEWORTHY: A. S. Ohlsen's contributions to histochemistry of stomach (*Compt. rend. trav. Lab. Carlsberg, ser chemi*, 23:331-479, 1941): Nobelate Swedish citizen A. Szent-Gyorgi's review of

muscle function (*Acta. Physiol. Scand.*, 9: Suppl. 25, 1945); G. Lundin's review of mechanical properties of cardiac muscle (*ibid.*, 7: Suppl. 20, 1944); T. Astrup's survey of blood coagulation (*ibid.*, Suppl. 21, 1944); J. Ambrosen's Geiger-Muller counter device for biological research (*ibid.*, 10:195, 1945); G. Birath's study of lung volume and ventilation efficiency in relation to collapse therapy in Tb (*Acta. Med. Scand.*, Suppl. 154, 1944); O. J. Broch's report on regulation of serum electrolytes and salt and water metabolism (*ibid.*, Suppl. 166, 1945) and K. A. Ekbom's description of "restless legs," characterized by paresthesia, pain and weakness (*ibid.*, Suppl. 158, 1945). E. Wang discusses thyroid influence on creatine metabolism (*ibid.*, Suppl. 169, 1946).

5. Also Notable: A. L. Lichtman and J. R. McDonald recommend polarizing microscope to note tissue birefringence variation in pathological states (*Arch. Path.*, 42:69, 1946). V. Zvetkov and others discuss birefringence of liquids in ultrasonic fields, which might be applied to fresh tissue (*Acta Physicochim* 21: 135, 1946). P. A. Kometiani and others show acetylcholine action in muscle is related to physiocochemical state of cytoplasmic substrate to which potassium is bound (*Biochim.*, 2:262, 1946). G. C. Brun shows arterial contraction after epinephrin is due to short peripheral axon reflexes (*Acta. Pharmacol. Tox.*, 1:403, 1945; 2:22, 1946). W. Wilbrandt ably discusses physiology of cell and capillary permeability (*Helv. Med. Acta.*, 13:143, 1946). F. W. Sunderman offers refreshing approach to study of edema and dehydration (*Am. J. Clin. Path.*, 16:353, 1946). J. Pollard and S. B. Stoker show that trauma releases local alkaline blood coagulant which is neutralized systemically by heparin (*Quart. J. Exp. Physiol.*, 33:267, 1946). L. C. D. Hermitte discusses venomous marine molluscs (*Trans. Roy. Soc. Trop. Med. Hyg.*, 39:485, 1946). E. G. Vassaf and V. R. Hall recommend 10 units insulin before meals in treating acute alcoholism (*New Eng. J. Med.*, 235:190, Aug. 8, 1946). W. Frei reviews factors in infectious epizootics (*Acta. Trop.*, 3:1, 1946). I. Abelin shows that cholesterol content of adrenals increases in narcosis (*Helv. Physiol. Pharmacol. Acta.*, 4:1, 1946). Our G. R. Herrmann reports on effects of decholesterizing agents on cholesterol levels in various diseases (*Texas S. J. Med.*, 42:260, 1946).

October, 1946

1. Antibiotics: H. J. Carlson and pals find buttercup extracts are antibiotic and sagebrush extracts are antimalarial (*J. Bact.*, 52:155, 1946). S. R. Bose isolates polyporin, selectively active antibiotic from *Polystictus sanguineus*, a genetically stable wood-rot fungus found in India (*Nature*, 158:292, Aug. 31, 1946). W. H. Wilkins continues search for antibiotic fungi and finds 10 very active species among wood-destroying Basidiomycetes (*Brit. J. Exp. Path.*, 27:140, 1946). M. I. Smith and others find streptomycin and promin synergize in inhibition of tubercle bacilli (*Proc. Soc. Exp. Biol. Med.*, 62:157, 1946). E. Wolinsky and W. Steenken

find streptomycin action reduced by increasing acidity and that streptomycin and penicillin resistance occur independently of each other (*ibid.*, p. 162).

2. GERIATRICS: P. C. Koller shows that nucleic acid reduction resulting from age, cold, disease or undernourishment hinders division of chromosome threads and may stop spermatogenesis (*Proc. Roy. Soc. B.*, 133:313, 1946). O. H. Lowry and others find no significant histochemical change in liver or brain with aging, but note decrease in relative mass of kidney cells (*J. Gerontol.*, 1:345, 1946). G. Kelemen notes increased tonsillar activity at onset of senescence like that at onset of puberty (*Geriatrics*, 1:277, 1946).

3. WORTHY VOLUMES: Clearly, wisely, briefly G. R. Stewart philosophizes in *Man: An Autobiography* (Random House, N.Y., 1946, 310 pp., $2.75). P. S. Hudson and R. H. Richens too politely show the silly fallacies of Lysenko's non-mendelian and dialectic genetics (*New Genetics in the Soviet Union*, Imp. Bur. Genetics, Cambridge, 1946, 88 pp., 6s). F. Weidenreich's *Apes, Giants and Man* implies question of size as criterion of biological excellence (Univ. Chicago Press, 1946, 129 pp., $2.50). D. E. Green edits useful *Currents in Biochemical Research* (Interscience, N.Y., 1946, 494 pp., $5). P. M. Symonds discusses *Dynamics of Human Adjustment* (Appleton, N.Y., 1946, 680 pp., $5). H. N. Wieman offers reconciliation of naturalism and religion in *The Source of Human Good* (Univ. Chicago Press, 1946, 319 pp., $3.50). E. T. Engle edits *The Problem of Fertility* (Princeton Press, 1946, 320 pp., $3.75). E. Herz and T. J. Putnam offer *Motor Disorders in Nervous Diseases*, with 10 long films (Columbia Univ. Press, N.Y., 1946, 192 pp., $3 book only). J. Hersey's medicinal and conscience-stirring account of A bomb at Hiroshima would make a WV (*New Yorker*, Aug. 31, 1946, whole issue, no cartoons). Less publicized than *General Education in a Free Society* (Harvard Press, Cambridge, 1945) but equally as significant is the *Report of the Curriculum Committee of the University of Wisconsin* (Madison, 1946, 138 pp., full bibliography).

4. PHARMACOLOGY: K. K. Chen and others report further on antispasmodic action of B-dimethyl-aminoethyl benzilate HCl (*Gastroenterol*, 7:213, 1946). R. R. Burtner summarizes synthetic antispasmodics (G. D. Searle, Chicago, 1946, 27 pp.). E. Frommel and others report that heavy metal salts tend to cause ascorbic acid depletion and blocking of cholinesterase (*Helv. Physiol. Pharmacol. Acta.*, 4:301–318, 1946). R. H. Moore and others study sulfonamide allergy in man showing necrosis of tissues involved with hyperactivity of reticulo-endothelium (*Am. J. Path.*, 22:703, 1946). E. J. Van Liere and others show how glucose inhibits gastric motility proportionally to amount present (*Gastroenterol*, 7:218, 1946). G. Hemmeler concludes that neither iron nor liver are helpful in anemias due to infections (*Helv. Med. Acta.*, 13:20–97, 1946). D. Lester and others give data on absorption, distribution and excretion of aspirin, showing 75 per cent excreted in urine in 15 to 30 hours (*J. Pharmacol. Exp. Therap.*, 87:329, 1946). Much data on di-isopropyl fluorophosphate (DFP), potent cholinesterase inhibitor, offered by W. Modell and others, R. G. Horton and others,

G. B. Koelle and A. Gilman (*ibid.*, 400, 414, 421, 435). Supplement of 125 pp. to this vol. devoted to British Anti-Lewisite (BAL), 2-3-dimercaptopropanol, of value in heavy metal poisoning.

5. ODDMENTS: G. Marsh and H. W. Beams demonstrate that growth direction of nerve fibers may be determined by electric current (*J. Cell. Comp. Physiol.*, 27:136, 1946). J. Trueta and others give data suggesting hypertension may result from disordered activity of nerve centers giving renal cortical ischemia and medullary congestion (*Lancet*, 2:237, Aug. 17, 1946). S. Lindsay and others find atheromatosis after diethylstibesterol (*Proc. Soc. Exp. Biol. Med.*, 62:315, 1946). R. W. Wissler and others offer more data showing adequate supply of essential amino acids necessary for antibody production (*ibid.*, p. 199). R. J. Rossiter tabulates three stages of recovery from severe protein deficiency, showing there is weight loss in the first stage (*Nature*, 158:304, Aug. 31, 1946). W. Schurer shows mast-cells and "heaped up" basophils are both heparin storage cells (*Helv. Med. Acta.*, 13:161, 1946). Our staff pot-boils locally, with W. A. Selle's note on physiological basis of asthma quite worthy (*Med. Rec. Ann.*, 40:1547–1570, 1946).

NOVEMBER, 1946

1. MORE BOOKS: R. J. Williams proposes new applied science, humanics, for comprehensive study of individual humans, in his *Human Frontier* (Harcourt Brace, N.Y., 1946, 314 pp., $3). E. A. Steinhaus helps in understanding of insect transmission of disease in his well prepared *Insect Microbiology* (Comstock, Ithaca, N.Y., 1946, 763 pp., $7.75). Physiologist W. A. Osborne collects his pleasant *Melbourne Argus* sketches and others in his *Essays and Studies* (Lothian Publ. Co., Melbourne, 1946, 195 pp., 10s 6d). J. R. Porter offers much in his *Bacterial Chemistry and Physiology* (Wiley, N.Y., 1946, $12). Important for tissue culturists are A. Fischer's *Essays* (Copenhagen, or Stechert, N.Y., 1946, 357 pp., 31s 6d). Among interesting *Monographs on the Progress of Research in Holland During the War* are H. Veldstra and others *Modern Development of Chemotherapy*, B. C. P. Jansen's *Nutrition Researches*, S. E. de Jongh's *Gonadotropic and Sex Hormones*, M. W. Woerdeman's *Experimental Embryology*, A. T. Knoppers' *Pharmacological Investigations*, and N. Waterman's *Modern Cancerology* (Elsevier Publ. Co., Amsterdam and N.Y., 1946, about 200 pp.). Sir A. Fleming well edits *Penicillin: Its Practical Application* (Blakiston, Phila., 1946, 380 pp., $7). M. R. Everett's *Medical Biochemistry* goes into well merited second edition (Hoeber, N.Y., 1946, 767 pp., $7). O. Saphir's *Autopsy Diagnosis and Technic* also comes to second edition (Hoeber, N.Y., 1946, 427 pp., $5). S. Licht lilts on *Music in Medicine* (New England Conservatory, Boston, 1946, 152 pp., $3). C. E. Benda discusses *Mongolism and Cretinism* (Grune & Stratton, N.Y., 1946, 325 pp., $6.50). M. Davis flies high in *Through the Stratosphere: The Human Factor in Aviation* (Mac-

millan, N.Y., 1946, 271 pp., $2.75). P. F. Russell and others offer *Practical Malariology* (Saunders, Phila., 705 pp., $8).

2. Symposia: A notable discussion on lymph, *Ann. N.Y. Acad. Sci.*, 46:679–882, 1946) includes R. Chambers and B. W. Zweifach on activity of blood capillary bed, E. M. Landis on capillary permeability, E. R. Clark on intracellular substance and tissue growth, P. D. McMaster on skin factors in lymph flow, V. Menkin on lymph blockade in immunity, C. K. Drinker on extravascular protein, W. E. Ehrich on the lymphocyte in lymph flow, and A. White and T. F. Dougherty on lymphocytes in globulin production. Discussion on aviation physiology (*Fed. Proc.*, 5:318–361) includes A. C. Ivy on high altitude problems, E. H. Wood and others on effects of acceleration in aviation, A. C. Burton on clothing and heat exchanges, H. K. Hartline on visual physiology, and M. I. Gregerson on shock. E. L. Tatum introduces discussion on neurospora as a biochemical tool (*ibid.*, pp. 361–389). E. A. Evans, E. G. Ball, L. Hellerman, W. B. Wendel and others discourse on biochemistry of malarial parasite (*ibid.*, pp. 390–407). Physiology in North America is interestingly surveyed by E. F. Adolph, P. Dow, T. E. Boyd, and J. H. Comroe (*ibid.*, pp. 407–436). Appropriate for the ether centennial is British tribute, with E. A. Underwood reviewing history, C. L. Hewer recent advances, J. H. Burns theories of anesthesia, A. C. King apparatus, and G. Liddle poetry (*Brit. Med. J.*, 2:525–542, Oct. 12, 1946).

3. And Also: F. H. Johnson and I. Lewin report quinine effects on dehydrogenases, temperature and pressure effects in disinfection and on growth rates of microbes (*J. Cell. Comp. Physiol.*, 28:1, 23, 47, 77, 1946). R. Andrew's article on dysenteries (*Med. J. Australia*, 2:289–311, Aug. 31, 1946) might well be booked, but section on amebiasis might well be revised. Relax: R. H. Follis finds no biological effects from high frequency radio waves (*Am. J. Physiol.*, 147:281, 1946). J. E. Davis produces hyperchromic anemia by acetylcholine and finds folic acid or liver extract increase cholinesterase action (*ibid.*, p. 404). M. Dixon and D. M. Needham concisely review British biochemical research on chemical warfare agents (*Nature*, 158:432, Sept. 28, 1946). M. F. Lockett isolates vasopressor base from dogs with renal ischemia, which seems to be same as base liberated by alkaline hydrolysis of healthy urine (*J. Physiol.*, 105:117, 126, 138, 1946). M. F. Murnaghan describes digitalis-like heart action and antidiuretic effect of penicillic acid (*J. Pharmacol. Exper. Therap.*, 88:119, 1946). A. M. Ambrose and F. DeEds report on parasympathetic stimulant action of antibiotic citronin (*ibid.*, p. 173). J. P. Duguid describes weakening of cell wall by penicillin (*Edin. Med. J.*, 53:401, 1946). E. R. Trethewie describes anticoagulant effect of spleen (*Austral. and New Zealand J. Surg.*, 15:286, 1946). W. Munch reviews pathological anatomy of acute cardiac syncope (*Acta. Path. Microbiol. Scan.*, 23:107, 1946). M. Delbruck reviews bacterial viruses or bacteriophages (*Biol. Rev. Cambridge Phil. Soc.*, 21:30, 1946). E. L. Way finds that barbitals antagonize lethal convulsive effects

of isonipicaine (demoral) but potentiate its depressant effect on respiration (*J. Pharmacol. Exp. Therap.*, 87:265, 1946). J. Stokes finds infectious hepatitis virus transmitted by fecal contamination (*Trans. Stud. Coll. Phys. Phila.*, 14:37, 1946). Our W. B. Sharp, M. B. John, and J. M. Robison discuss etiology of otomycosis (*Texas St. J. Med.*, 42:380, 1946).

END OF 1946

1. ANTIBIOTICS: V. du Vigneaud and others synthesize penicillin by condensing a benzyl oxazolone with penicillamine, giving basis for synthesis of many types of penicillins (*Science*, 104:431, Nov. 8, 1946). R. Brodersen and A. Kjaer report antibacterial action, low toxicity, and inactivation by SH of such unsaturated lactones as dicoumarol (*Acta. Pharmacol Toxicol*, 2:109, 1946). B. Kromann reports oil-in-water emulsion of 250 units (Florey) penicillin per Gm. cream is optimal for local application to infected wounds (*ibid.*, p. 185). N. Atkinson finds antibacterial activity, even against acid fast types, in watery extracts of mushroom fungi as Psalliota xanthoderma and Cortinarius rotundisporus (*Austral. J. Exp. Biol. Med.*, 24:169, 1946).

2. ANESTHESIA CENTENNIAL: Important contributions are: H. H. Young, Crawford W. Long (*Bull. Hist. Med.*, 12:191–225, 1942); H. R. Raper, Long Centennial Celebrations (*ibid.*, 13:340–356, 1943); W. H. Archer, Horace Wells Life and Letters (*J. Am. Coll. Dentists*, 11:81–218, 1944); Horace Wells Centenary (*Conn. S. Med. J.*, 8:725–802, 1944); T. E. Keys, History of Surgical Anesthesia (Schuman, N.Y., 1945); H. R. Raper, Men Against Pain (Prentice-Hall, N.Y., 1945); E. S. Ellis, Ancient Anodynes (Heinemann, London, 1946); V. Robinson, Victory over Pain (Schuman, N.Y., 1946); J. F. Fulton and M. E. Stanton, The Centennial of Surgical Anesthesia (Schuman, N.Y., 1946); Anesthesia Centennial Number (*J. Hist. Med. Allied Sci.*, 1:505–676, 1946); Centenary of Anesthesia Number (*Brit. Med. Bull.* 4:81–155, 1946); Anesthesia Number (*Brit. Med. J.*, (2):525–547, Oct. 12, 1946); Anesthesia Number (*Irish J. Med. Sci.*, 6 ser., No. 250,644–723, 1946); B. M. Duncan, Development of Inhalation Anesthesia (Oxford Univ. Press, for Wellcome Historical Medical Museum, London, 1946). More next year!

3. BLOOD: A. Lambrecht and others find more than 500 basophiles per million erythrocytes needed to justify diagnosis of lead poisoning (*Acta Clin. Belgica*, 1:224, 1946). M. Ostro and D. I. Macht report improvement in hemophilia from spleen radiation (*South. Med. J.*, 39:860, 1946). D. F. Cappell offers helpful clinical review of Rh blood group (*Brit. Med. J.*, 2:601, 641, Oct. 26, Nov. 2, 1946). A. S. Wiener and P. Levine discuss Rh factor (*Am. J. Clin. Path.*, 16:477, 597, 1946).

4. NOBELATION: H. J. Muller, while at Texas, for gene mutation with X-ray (*Genetics* 13:279–357, 1928; with T. S. Painter, *Am. Naturalist*, 63:193–200, 1929, also pp. 481–486); J. B. Sumner at Cornell for isolating and crystallizing enzyme urease (*J. Biol. Chem.*, 69:435–441, 1926); J. H. Northrop at Rockefeller Princeton for isolating and crystallizing

pepsin and trypsin, and work on bacteriophage (*J. Gen. Physiol.*, 13:739, 1930, 16:267, 1932; *Physiol. Rev.*, 17:144, 1937; *J. Gen. Physiol.*, 21:335–366, 1938), and W. M. Stanley for isolating and crystallizing viruses (*Science*, 81:644, 1935; *Ergebn. Physiol.*, 39:294–347, 1937, and *Bull. N.Y. Acad. Med.*, 14:398–428, 1938).

5. WORTHY: J. Erlanger and G. M. Schoepfle study nerve degeneration and regeneration (*Am. J. Physiol.*, 147:550, 1946). E. W. Page, our E. Ogden, and E. Anderson find cortical steroids restore renal hypertension in hypophysectomized rats while testosterone and estradiol are lethal (*ibid.*, 471). J. P. Greenstein and others report nucleic acid metabolism and degradation (*J. Nat. Cancer Inst.*, 7:9–29, 1946). J. Drummond is provocative in his theory of intracellular energy production and its practical applications in cardio-vascular conditions (*S. African Med. J.*, 20:596, 1946). R. Straus and others confirm Russian claims that antireticular cytotoxic serum speeds healing of fractures (*J. Immunol.*, 54:151–178, 1946). L. E. A. Wright and V. M. Trikojus explain action of iodine in Graves's disease by finding it inactivates thyreotropic hormone (*Med. J. Austral.*, 2:541, Oct. 19, 1946). U. Savonheimo reviews clinical actinomycosis (*Ann. Med. Int. Fenniae*, 35:74, 1946). C. de Duve and J. P. Boucharet propose general theory of insulin action (*Arch. Internat. Pharmaco.*, 72:62, 1946). J. E. Davis and D. E. Fletcher report hyperchromic anemia and nervous system changes caused by daily giving of choline (*J. Pharmacol. Exp. Therap.*, 88:246, 1946). O. Krayer and others find helpful cardiac effects from alkanolamines (*ibid.*, 277). W. Raab and R. J. Humphreys say dibenzylchlorethylamine protects heart against fatal dose of epinephrin (*ibid.*, 268). A. G. H. Bjurstedt studies chemoreflex and centrogenic control of breathing during oxygen deficiency (*Acta. Physiol. Scand.*, 12: Suppl., 38, 1946). H. Fischer makes fundamental study of cellular respiration effects of alkaloids (*Arch. Exp. Path. Pharmakol*, 200:455, 1943; *Helv. Physiol. Pharmacol. Acta.*, 4:423, 1946). G. V. Pillmore offers useful *Clinical Radiology* (Davis, Phila., 2 vols., 850 and 708 pp., 1946, $45). Vol. 21 *Acta. Psych. Neurol.* is dedicated to Hjalmar Helwig on his 60th birthday, 1946. J. W. Grott and others (Warsaw) find high exalic and uric acid levels in patients with musculo-articular pain (*Acta. Med. Scand.*, 125:576, 1946). H. Heusser discusses traumatic aspects of operative procedures (*Helv. Chir. Acta.*, 13:167, 1946). Our A. O. Singleton and J. C. Kennedy recommend physiological principles in surgery (*Texas S. J. Med.*, 42:411, 1946).

TEXAS REPORTS ON BIOLOGY AND MEDICINE

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